The association between preterm labour, perinatal mortality and infant death (during the first year) in Bishop Lavis, Cape Town, South Africa

L T Brink, MSc; **G S Gebhardt**, MB ChB, MMed, FCOG (SA), MSc (Med Sci), PhD; **D Mason**, MB ChB;
C A Groenewald, MB ChB, MMed, FCOG (SA), MCom; **H J Odendaal**, MB ChB, MMed, FCOG (SA), MD, FRCOG

Department of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

Corresponding author: *H J Odendaal (hjo@sun.ac.za)*

Background. We present further analyses from the Safe Passage Study, where the effect of alcohol exposure during pregnancy on sudden infant death syndrome and stillbirth was investigated.
Objectives. To describe pregnancy and neonatal outcome in a large prospective study where information on the outcome of pregnancy was known in >98.3% of participants and ultrasound was used to determine gestational age (GA).
Methods. As part of the Safe Passage Study of the PASS Network in Cape Town, South Africa, the outcomes of 6 866 singleton pregnancies were prospectively followed from recruitment in early pregnancy until the infant was 12 months old to assess pregnancy outcome. Fetal growth was assessed by *z*-scores of the birth weight, and GA at birth was derived from early ultrasound assessments. The effects of fetal growth restriction and preterm delivery on pregnancy outcome were determined.
Results. There were 66 miscarriages, 107 stillbirths at ≥22 weeks' gestation, 66 stillbirths at ≥28 weeks' gestation, 29 and 18 neonatal deaths at ≥22 and ≥28 weeks' gestation, respectively, and 54 post-neonatal deaths (28 days - 12 months). The miscarriage rate was 9.6/1 000 and the infant mortality rate 12.4/1 000. Of the births, 13.8% were preterm. For deliveries at ≥22 and ≥28 weeks, the stillbirth rates were 15.7 and 9.8/1 000 deliveries, respectively. For deliveries at ≥22 and ≥28 weeks, the neonatal death rates were 4.3 and 2.7/1 000 live births, respectively. For these pregnancies the perinatal mortality rates were 20.0/1 000 (≥22 weeks) and 12.5/1 000 (≥28 weeks), respectively. Only 15.9% of stillbirths occurred during labour (in 15.9% of cases it was uncertain whether death had occurred during labour). In the majority of cases (68.2%) fetal death occurred before labour, and 82.2% of stillbirths and 62.1% of neonatal deaths occurred in deliveries before 37 weeks. Including the miscarriages, stillbirths and infant deaths, there were 256 pregnancy losses; 77.3% were associated with deliveries before 37 weeks. Only 1.8% of all the women were HIV-positive, whereas the HIV-positive rate was 3.7% among those who had stillbirths. Birth weight was below the 10th centile in 25.6% of neonatal and post-neonatal deaths compared with 17.7% of survivors.
Conclusions. Preterm birth and fetal growth restriction play significant roles in fetal, neonatal and infant losses.

S Afr Med J 2019;109(2):xxxx. DOI:10.7196/SAMJ.2019.v109i2.13438

To the best of our knowledge, no information is available on perinatal, neonatal and infant mortality rates based on gestational age (GA) at delivery for any community-based cohort in South Africa (SA). In addition, birth weight is commonly used to define the lower borders of fetal viability. To distinguish between a late miscarriage and an early stillbirth, a birth weight of 500 g rather than GA of 22 weeks is often used. However, in defining stillbirth, GA is the preferred criterion with regard to the lower cut-off point, as using birth weight may exclude growth-restricted fetuses.[1]

Furthermore, patients are often discharged from the delivery unit very early, and it is therefore unlikely that all neonatal deaths after discharge are accurately reported. There is also no information on the rates of late miscarriages, as this information is not prospectively collected.

The true incidence of mid-trimester miscarriage is unknown.[2] Information on the incidence and causes of miscarriages may provide valuable information for programmes to reduce stillbirths. It is also necessary to analyse stillbirth and perinatal mortality rates (PNMRs) regularly to predict whether the Sustainable Development Goals for 2030 will be reached.[3]

The Safe Passage Study (SPS) was undertaken in three populations, of which the 'coloured' (mixed race) population in Bishop Lavis, a suburb of Cape Town, SA, was one, to determine the role of alcohol consumption in stillbirths and sudden infant deaths.[4] Robust information on all pregnancies, from the first antenatal visit until the infant was 1 year old, allowed accurate calculation of perinatal and infant mortality. It also created an opportunity to calculate late miscarriage rates for participants who booked early and to study the role of preterm delivery in perinatal mortality and infant deaths during the first year.

Objectives

To determine the true population-based risk of miscarriage, late stillbirth, neonatal death and preterm delivery in otherwise low-risk coloured pregnant women in a suburban area of Cape Town.

Methods

This prospective cohort study was conducted in Bishop Lavis. Recruitment was done between August 2007 and January 2015. A woman was eligible if all the following criteria were met: (*i*) able to provide informed consent; (*ii*) pregnant with one or two fetuses; (*iii*) ≥16 years of age; (*iv*) GA of at least 6 weeks and 0 days and not at the delivery admission unit; and (*v*) able to speak English or Afrikaans. A woman was excluded if any of the following

criteria were met: (*i*) planned abortion; (*ii*) planned relocation from catchment area prior to delivery; or (*iii*) advice against participation by a healthcare provider (e.g. additional medical care required).

A total of 7 060 pregnant women were recruited at the antenatal clinics. Determination of GA was done by ultrasound at the first or before the second antenatal visit. A trained midwife or experienced ultrasonographer performed all the ultrasound examinations. For this analysis we selected only the 7 010 singleton pregnancies (Fig. 1). There were no exclusions for any medical conditions.

At the recruitment visit, participants provided informed consent, which included consent for collection of the placenta for histological examination after delivery. Alcohol use and cigarette smoking were determined in detail at up to four occasions during pregnancy as described by Dukes *et al*.[4]

After a fetal death, separate informed consent was obtained for autopsy.[5] Research midwives checked labour ward admissions and deliveries daily to determine whether a study participant had delivered. In cases of fetal death, the social worker and/or senior study personnel were alerted to provide support and bereavement counselling, and discussed consent for autopsy at an appropriate time.

All deaths were presented and discussed at the weekly perinatal mortality meetings of the hospital, which were attended by obstetricians, neonatologists, pathologists, geneticists, fetal and maternal subspecialists and midwives. A primary cause of death was assigned and coded using the classification system of the Perinatal Problem Identification Programme (PPIP).[6]

The World Health Organization's definition of stillbirth was used for the study (a baby born with no signs of life at or after 28 weeks' gestation).[7] The definition used for stillbirth in high-income countries (death at or after 22 weeks) was used to classify an early stillbirth.[8] There were therefore three groups of different outcomes: miscarriage (pregnancy loss from recruitment to <22 weeks), early stillbirth (fetal death 22 weeks 0 days - 27 weeks 6 days), and late stillbirth (fetal death at ≥28 weeks). As death sometimes occurred before 22 (or 28) weeks but delivery only after these GAs, the deaths before 22 (or 28) weeks were excluded from the respective study group but used for the earlier gestation group. GA in all stillbirths was assessed individually by comparing GA at delivery (as determined by ultrasound at booking), date of last fetal heart rate (FHR) recording, and measurement of the foot length at autopsy.[9] Any death where a FHR was recorded at or after 22/28 weeks was regarded as a stillbirth, irrespective of the birth weight. To establish whether the fetal death occurred before or during labour, clinical information such as detection of a fetal heartbeat at admission for labour or during labour and autopsy findings such as maceration of the fetal skin were used.[10] Clinical judgement was used in cases where it was difficult to determine whether death had occurred during early labour before the participant was admitted to hospital.

In the case of live births, contact with the mother and infant was maintained after discharge as the infant was brought back to the research unit within the first 5 days of life, at ~1 month of age, and finally at the age of 1 year. If any of these visits were missed, the mother was contacted to enquire about the condition of the infant. Deaths up to 28 days after birth were regarded as neonatal deaths. Post-neonatal (infant) death was defined as death between the age of 28 days and 366 days.[11] Reference values on the Intergrowth-21 study were used to determine whether the newborns weighed below the 10th percentile.[12]

Statistical analysis

Data were entered in Excel 365 (Microsoft, USA) and then coded and exported for analysis in Stata 14 (StataCorp, USA). Analyses were performed using SAS/STAT software, version 9.3 (SAS Institute, USA). Descriptive statistics were used to describe continuous variables. As some of the findings were not normally distributed, both the mean and median values were calculated. The χ^2 test was used to determine significance in categorical data.

Ethics approval

Permission to conduct the study was obtained from the Health Research Ethics Committee of Stellenbosch University (ref. no. N06/10/210).

Results

The recruited cohort consisted of 6 866 women with singleton pregnancies (caesarean section rate 13.0%), of whom 6 170 (89.8%) brought their infants for the final follow-up visit at the age of 1 year (Fig. 1).

There were 66 miscarriages that occurred after the diagnosis of pregnancy was made, giving a cumulative incidence of 9.6/1 000 deliveries over the study period (Table 1). Of the 2 724 women with singleton pregnancies who enrolled between 14 weeks 0 days and 21 weeks 6 days, 20 had miscarriages, giving a mid-trimester miscarriage rate of 7.3/1 000 pregnancies.

There were 107 stillbirths at or after a GA of 22 weeks, presenting a risk (or cumulative incidence) of 15.7/1 000; of these stillbirths, 66 occurred at or after a GA of 28 weeks, for a risk (cumulative incidence) of late stillbirths of 9.8/1 000 (Table 1).

Of the 107 stillbirths, 88 (82.2%) were before 37 weeks and 73 (68.2%) before 34 weeks. In 17 (15.9%) of the stillbirths, death occurred during labour. The mean GA at enrolment for the 107 stillbirths was 18 weeks and 5 days, compared with a mean GA of 20 weeks and 1 day for all births in the study. The mean GA at delivery for the stillbirths was 30 weeks 4 days, compared with 38 weeks 4 days for all births in the study (Table 2).

Intrapartum deaths occurred in 17 (15.9%) of the 107 stillbirths; in 17 (15.9%) it was uncertain when the death had occurred and in 73 (68.2%) it was before labour.

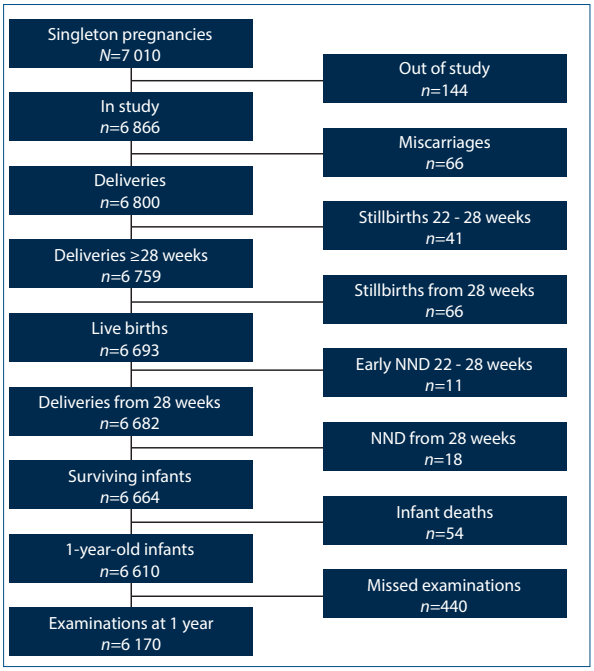

Fig. 1. Flowchart of pregnancies and deliveries. (NND = neonatal death.)

Table 1. Pregnancy and infant losses for singleton pregnancies

	Miscarrige	Stillbirth ≥22 weeks	Stillbirth ≥28 weeks	Neonatal death ≥22 weeks	Neonatal death ≥28 weeks	Perinatal death ≥22 weeks	Perinatal death ≥28 weeks	Postnatal death	Infant death	Fetal and infant death
All losses, *N**	66	107	66	29	18	136	84	54	83	190
Totals, *N*	6 866	6 800	6 759	6 693	6 682	6 800	6 759	6 664	6 693	6 800
Rate, /1 000	9.6	15.7	9.8	4.3	2.7	20.0	12.5	8.1	12.4	28.1
Losses delivered before 34 weeks, *n* (%)	n/a	73 (68.2)	32 (48.5)	16 (55.2)	5 (27.8)	89 (65.4)	37 (44.1)	17 (31.5)	33 (39.8)	106 (55.8)
Losses delivered before 37 weeks, *n* (%)	n/a	88 (82.2)	47 (71.2)	18 (62.1)	7 (38.9)	106 (77.9)	54 (64.3)	26 (48.2)	44 (53.0)	132 (69.5)

n/a = not applicable.
*All losses used as denominator for calculation of %.

There were 29 neonatal deaths before 28 days after delivery, giving a neonatal death rate of 4.3/1 000 live births for deliveries at ≥22 weeks and 2.7/1 000 live births for deliveries at ≥28 weeks. The PNMR was therefore 20.0/1 000 for deliveries from 22 weeks and 12.5/1 000 for deliveries from 28 weeks (Table 1). Sixteen (55.2%) of these neonates were delivered before 34 weeks. Twenty-five (86.2%) of the neonates died before discharge from hospital.

Fifty-three (98.2%) of the 54 infant deaths from 28 days to the age of 1 year occurred after discharge from hospital. Twenty-six (48.2%) of the post-neonates were born before 37 weeks and 17 (31.5%) before 34 weeks. The mean GA at enrolment for the neonates was 20 weeks 1 day (the same as for all subjects in the study), compared with 21 weeks 5 days for infant deaths. The mean GA at delivery for neonatal deaths was 32 weeks 3 days, compared with 36 weeks 0 days for infants who died at 28 days or later (Table 2).

HIV status was known for all women whose fetuses or infants died. Three (4.6%) of the 66 women who had miscarriages were HIV-positive. Four (3.7%) of the 107 women who had stillbirths were HIV-positive. None of the 29 women who had neonatal deaths was HIV-positive, in contrast to 3 (5.6%) of the 54 women who had post-neonatal deaths. In total, only 122 (1.8%) of the 6 866 women with singleton pregnancies were HIV-positive.

There were 256 pregnancy losses, consisting of 66 miscarriages, 107 stillbirths and 83 infant (neonatal and post-neonatal) deaths (Fig. 1); 132 (69.5%) fetal and infant deaths were associated with deliveries before 37 weeks, and this percentage rose to 77.3% when miscarriages were included.

Preterm delivery (before 37 weeks) occurred in 13.8% of pregnancies, and the mean (median) GA was 240 (248) days. Delivery before 34 weeks occurred in 271 cases (4.0%); the mean (median) GA was 212 (220) days. The mean (median) GA for the 5 865 term pregnancies (≥37 weeks) was 276 (276) days (39 weeks 3 days) (Table 2).

Birth weight was below the 10th centile in 25.6% of infants who died, as opposed to 17.7% of survivors. Birth weight was below the 10th centile in 18.1% (1 210/6 691) of newborns. Newborns with a birth weight below the 90th centile accounted for 5.5% of deliveries.

At recruitment, a body mass index (BMI) of <18 kg/m^2 was observed in 3.3% of pregnant women. Their mean BMI was 17.1 kg/m^2 (range 13.7 - 17.99). Fifty-four (25.5%) of these women delivered small-for-gestational-age (SGA) babies, 72.2% delivered appropriate-for-gestational-age (AGA) babies, and 2.4% delivered large-for-gestational-age (LGA) babies. Only 52.8% of women had a normal BMI (18 - 25 kg/m^2), of whom 21.6% had SGA, 75.7% AGA and 2.7% LGA babies. A BMI >25 kg/m^2 was observed in 44.0% of women, of whom 13.1% delivered SGA, 77.6% AGA and 9.3% LGA babies. These frequencies differed significantly (Pearson χ^2 = 199.0650, df = 4; p<0.0001).

Discussion

Longitudinal studies are essential to examine the effects of environmental conditions on birth outcome.[13] Such studies would be of great value to investigate the late complications of preterm delivery or address late abortion, as this information is not routinely collected. Depending on the prevalence of the condition studied, the size of longitudinal cohorts can vary from 800 to 100 000.[14] Our large sample size (6 866 participants) is sufficient to allow meaningful analysis of pregnancy complications.

We found a miscarriage rate of 9.6/1 000, but for mid-trimester miscarriages, it was 7.3/1 000 in the 2 724 pregnancies followed from 14 weeks' gestation. The miscarriage rates of 7.3 - 9.6/1 000 are very similar to the stillbirth rate of 9.8/1 000 we have found for pregnancies at or after 28 weeks' gestation. The burden of late miscarriage is therefore considerable.

To reduce the number of stillbirths, conditions associated with late mid-trimester miscarriages should also be addressed. Sending the placenta for histological examination after late mid-trimester miscarriage should provide valuable additional information. As there are few publications on the causes of mid-trimester miscarriages,[15-17] more studies investigating their causes should be done.

We found a stillbirth rate of 9.8/1 000 for deliveries at or after 28 weeks. The estimated worldwide stillbirth rate for deliveries at or after 28 weeks is 18.4/1 000. The highest rates reported were in south-eastern Asia and sub-Saharan Africa (SSA), at 25.5 and 28.7/1 000, respectively.[3] For SA the rate was 17.6/1 000 in 2012 and 2013, according to the Saving Babies Report.[18] For the Western Cape Province the most recent rate was 12.3/1 000.[18] For the coloured population served by Tygerberg Hospital the latest available rate was 12.6/1 000 in 2011.[19] The rate of 9.8/1 000 in Bishop Lavis therefore compares very favourably with other rates in low-income countries and other rates in the Western Cape. It also compares favourably with the goals of the Every Newborn Action Plan, where the target is ≤12 stillbirths per 1 000 deliveries.[20] In addition, it compares favourably with the highest stillbirth rates in high-income countries, such as the rates of 7.9 and 8.8 in Moldova and Ukraine, respectively.[21]

In SSA, it is estimated that 51% of stillbirths occur during labour.[3] In a large study consisting of >200 000 women from 106 communities

Table 2. Gestational ages at enrolment and delivery

Category	Gestational age at enrolment (days), mean (median)	Gestational age at delivery (days), mean (median)
All in study (*N*=6 866)	141 (140)	270 (274)
Stillbirths (*n*=107)	131 (130)	214 (212)
Neonatal deaths (*n*=29)	141 (138)	227 (227)
Postnatal deaths (*n*=54)	152 (145)	252 (259)
Preterm deliveries, <37 weeks (*n*=935)	141 (140)	240 (248)
Very preterm deliveries, <34 weeks (*n*=271)	130 (128)	212 (220)
Term pregnancies, ≥37 weeks (*n*=5 865)	142 (141)	276 (276)

in seven sites in six low-income countries, ~70% of stillbirths were probably intrapartum.[22] The rate of 15.9% in the present study is therefore indicative of good care during labour and delivery.

Nutrition and potentially modifiable lifestyle conditions, each contributing 10%, were associated with stillbirths.[3] Gray *et al.*[23] examined the records of >500 000 singleton live births and 2 699 stillbirths in Scotland from 1994 to 2003. Smoking during pregnancy accounted for 38% of the social inequality in stillbirths and 31% of inequalities in infant deaths. As smoking and drinking alcohol were associated with stillbirths in the Bishop Lavis cohort,[2] efforts to address these unhealthy lifestyle factors should reduce the stillbirth rate further.

We found a stillbirth/neonatal death ratio of 3.7 for deliveries at ≥22 weeks or ≥28 weeks. This does not compare favourably with reported ratios. In a study in 24 countries, addressing 1 134 stillbirths at >28 weeks' gestation and 1 465 neonatal deaths at >24 weeks, a ratio of 0.8 was found.[24] This is very similar to the ratio of 1.2 in a study in 106 communities in seven sites in six low- and middle-income countries where 97.2% of the 220 235 enrolled women completed follow-up.[23] A ratio of 1.03 was reported in a study of 8 230 women in four rural health districts in the Democratic Republic of the Congo.[25] In the assessment of 2 656 000 stillbirths and 3 072 000 neonatal deaths in 193 countries, all United Nations members, it was found that the stillbirth/neonatal death ratio for 2010 was 0.86.[26] A high ratio was found in a hospital in Uganda, where there were 430 stillbirths and 80 neonatal deaths, producing a ratio of 5.4.[27]

Only 1.8% of our participants were HIV-positive. The estimated overall HIV prevalence rate is 12.6% for the total SA population; the total number of people living with HIV was estimated at 7.06 million in 2017. For females aged 15 - 49 years, an estimated 21.2% of the population is HIV-positive.[28] According to another study, the prevalence for women aged 15 - 49 years is 23.3%.[29] The reasons for the low prevalence rate in our study are unclear. It is most likely that exposure to HIV among pregnant women in this community is low, but it is also possible that a higher resistance to HIV could have played a role.[30,31]

When compared with international standards,[12] the 18.1% prevalence of SGA in our local community-based cohort is high, but it is lower than the rate of 25.5% reported for SSA.[32] Of the liveborn babies who died after delivery, 25.6% had a birth weight below the 10th centile, in contrast to 17.7% for newborns who were alive at 1 year. The odds ratio for dying after delivery for SGA infants was 1.87 (95% confidence interval (CI) 1.144 - 3.066; $p<0.05$). This is in keeping with the finding of Aiken[33] that SGA infants have increased perinatal morbidity and mortality. Compared with AGA babies, SGA infants are also at risk for long-term sequelae that include poor neurodevelopmental scores such as motor skills, vision and hearing, low educational attainment and neurological morbidity (including cerebral palsy).[33] Long-term follow-up of SGA infants is therefore essential.

When suboptimal growth is suspected, umbilical artery Doppler assessment is recommended to differentiate between fetuses thought to be 'constitutionally small' and those with fetal growth restriction due to placental insufficiency, which is associated with many risks.[34] However, diagnosing fetal growth restriction, even in well-resourced countries, remains difficult.[34] Various strategies have been investigated to increase the yield of prenatal diagnosis, all with only limited success. It seems that the use of flow velocity in the middle cerebral artery may be helpful to identify at-risk fetuses not identified by other methods.[35] Our study highlights the importance of identifying SGA in order to prevent perinatal morbidity and mortality. However, the way forward in a low-income country is difficult. There is a high prevalence of many social confounders such as poverty, smoking, alcohol and illicit drug use and poor nutrition that contribute to a suboptimal intrauterine environment, and all need to be addressed.

Preterm delivery is a worldwide problem. According to 20 cohorts, providing data for >2 million live births from Asia, Africa and Latin America, the pooled overall relative risk for neonatal mortality from preterm delivery was 6.82 (95% CI 3.56 - 13.07). Although preterm birth affects fewer neonates than SGA does, it is associated with a higher mortality risk.[36] We found a preterm delivery rate of 13.8%, which is higher than the 2010 rate of 12.3% for SSA.[32] The high preterm delivery rate is probably one of the reasons for a decrease of only 1.5% per year in neonatal mortality for SSA from 2000 to 2010.[26] The high preterm delivery rate for SSA is in sharp contrast to the low rate of 5.4 - 8.9% for 24 European countries in 2010.[24]

Conclusion

Key findings in our study were the high rates of mid-trimester abortions, preterm deliveries and SGA infants, as well as the high stillbirth/neonatal death ratios. As only 15.9% of stillbirths occurred during labour and the maceration rate was 52%,[9] the underlying causes are more likely to be related to placental and environmental conditions than to poor care during and after delivery. Environmental conditions such as cigarette smoking and excessive use of alcohol associated with the increased risks of mid-trimester abortion, stillbirth and preterm birth should therefore be addressed in the pursuit of reducing perinatal mortality.

Declaration. This publication was one of the requirements for a PhD for the first author (LTB).

Acknowledgements. We are grateful to all the other members of the SPS for collection of data.

Author contributions. LTB extracted the required clinical information

from the database, designed the tables and figure, provided information to calculate the *z*-scores, performed quality control of the data, contributed to the writing, and checked the data at the end. GSG co-ordinated perinatal mortality meetings, helped with the statistical analysis, contributed to the writing, and proofread the manuscript several times. DM co-ordinated perinatal mortality meetings, contributed to the writing, and proofread the manuscript several times. CAG was manager of the study, performed quality control of the data, and contributed to editing of the manuscript. HJO was principal investigator of the study, designed the study, initiated the manuscript, wrote the initial draft, and contributed to editing.

Funding. The study was funded by the National Institute on Alcohol Abuse and Alcoholism, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Institute on Deafness and Other Communication Disorders (U01 HD055154, U01 HD045935, U01 HD055155, U01 HD045991 and U01 AA016501).

Conflicts of interest. None.

1. Lawn JE, Gravett MG, Nunes TM, Rubens CE, Stanton C. Global report on preterm birth and stillbirth (1 of 7): Definitions, description of the burden and opportunities to improve data. BMC Pregnancy Childbirth 2010;10(1):S1. https://doi.org/10.1186/1471-2393-10-S1-S1
2. McNamee KM, Dawood F, Farquharson RG. Mid-trimester pregnancy loss. Obstet Gynecol Clin North Am 2014;41(1):87-102. https://doi.org/10.1016/j.ogc.2013.10.007
3. Lawn JE, Blencowe H, Waiswa P, et al. Stillbirths: Rates, risk factors, and acceleration towards 2030. Lancet 2016;387(10018):587-603. https://doi.org/10.1016/S0140-6736(15)00837-5
4. Dukes KA, Burd L, Elliott AJ, et al. The Safe Passage Study: Design, methods, recruitment, and follow-up approach. Paediatr Perinat Epidemiol 2014;28(5):455-465. https://doi.org/10.1111/ppe.12136
5. Odendaal HJ, Elliott A, Kinney HC, et al. Consent for autopsy research for unexpected death in early life. Obstet Gynecol 2011;117(1):167-171. https://doi.org/10.1097/AOG.0b013e318200cb17
6. Perinatal Problem Identification Program. https://www.ppip.co.za/ (accessed 31 December 2018).
7. World Health Organization 2016. Stillbirths. 2016. http://www.who.int/maternal_child_adolescent/epidemiology/stillbirth/en/ (accessed 3 September 2017).
8. Hure AJ, Powers JR, Mishra GD, Herbert DL, Byles JE, Loxton D. Miscarriage, preterm delivery, and stillbirth: Large variations in rates within a cohort of Australian women. PLoS One 2012;7(5). https://doi.org/10.1371/journal.pone.0037109
9. Geldenhuys E, Coldrey J, Wright C, et al. Fetal foot length at delivery as a tool for determining gestation length in non-macerated stillbirths. Int J Gynecol Obstet 2017;138(1):107-112. https://doi.org/10.1002/ijgo.12177
10. Genest DR, Singer DB. Estimating the time of death in stillborn fetuses: III. External fetal examination; a study of 86 stillborns. Obstet Gynecol 1992;80(4):593-600.
11. Kamath-Rayne BD, Defranco EA, Chung E, Chen A. Subtypes of preterm birth and the risk of postneonatal death. J Pediatr 2013;162(1):28-34e2. https://doi.org/10.1016/j.jpeds.2012.06.051
12. Papageorghiou AT, Ohuma EO, Altman DG, et al. International standards for fetal growth based on serial ultrasound measurements: The Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet 2014;384(9946):869-879. https://doi.org/10.1016/S0140-6736(14)61490-2
13. Golding J, Jones R, Preece A, Bruné M, Pronczuk J. Choice of environmental components for a longitudinal birth cohort study. Paediatr Perinat Epidemiol 2009;23(s1):134-153. https://doi.org/10.1111/j.1365-3016.2009.01014.x
14. Golding J, Steer C. How many subjects are needed in a longitudinal birth cohort study? Paediatr Perinat Epidemiol 2009;23(s1):31-38. https://doi.org/10.1111/j.1365-3016.2008.00997.x
15. Greenwood DC, Alwan N, Boylan S, et al. Caffeine intake during pregnancy, late miscarriage and stillbirth. Eur J Epidemiol 2010;25(4):275-280. https://doi.org/10.1007/s10654-010-9443-7
16. Mazzucconi MG, de Sanctis V, Alfo M, et al. Maternal thrombophilia and adverse pregnancy outcome: A case-control study. Acta Haematol 2015;133(2):242-248. https://doi.org/10.1159/000363048
17. Ball E, Bulmer J, Ayis S, Lyall F, Robson S. Late sporadic miscarriage is associated with abnormalities in spiral artery transformation and trophoblast invasion. J Pathol 2006;208(4):535-542. https://doi.org/10.1002/path.1927
18. Perinatal Problem Identification Program. http://www.ppip.co.za/wp-content/uploads/Saving-Babies-2012-2013 (accessed 31 December 2018).
19. Odendaal HJ, Gebhardt GS, Theron GB. Stillbirth rates in singleton pregnancies in a stable population at Karl Bremer and Tygerberg hospitals over 50 years. S Afr J Obstet Gynaecol 2013;19(3):67-70. http://www.sajog.org.za/index.php/SAJOG/article/view/662/406 (accessed 4 January 2019).
20. Qureshi ZU, Millum J, Blencowe H, et al. Stillbirth should be given greater priority on the global health agenda. BMJ 2015;351:h4620. https://doi.org/10.1136/bmj.h4620
21. Flenady V, Wojcieszek AM, Middleton P, et al. Stillbirths: Recall to action in high-income countries. Lancet 2016;387(10019):691-702. https://doi.org/10.1016/S0140-6736(15)01020-X
22. Saleem S, McClure EM, Goudar SS, et al. A prospective study of maternal, fetal and neonatal deaths in low-and middle-income countries. Bull World Health Organ 2014;92(8):605-612. https://doi.org/10.2471/BLT.13.127464
23. Gray R, Bonellie SR, Chalmers J, et al. Contribution of smoking during pregnancy to inequalities in stillbirth and infant death in Scotland 1994 - 2003: Retrospective population based study using hospital maternity records. BMJ 2009;339:b3754. https://doi.org/10.1136/bmj.b3754
24. Zeitlin J, Mortensen L, Cuttini M, et al. Declines in stillbirth and neonatal mortality rates in Europe between 2004 and 2010: Results from the Euro-Peristat project. J Epidemiol Community Health 2016;70(6):609-615. https://doi.org/10.1136/jech-2015-207013
25. Engmann C, Matendo R, Kinoshita R, et al. Stillbirth and early neonatal mortality in rural Central Africa. Int J Gynecol Obstet 2009;105(2):112-117. https://doi.org/10.1016/j.ijgo.2008.12.012
26. Lawn JE, Kinney MV, Black RE, et al. Newborn survival: A multi-country analysis of a decade of change. Health Policy Plan 2012;27(Suppl_3):iii6-iii28. https://doi.org/10.1093/heapol/czs053
27. Moyer CA, Kolars CK, Oppong SA, Bakari A, Bell A, Busingye P. Predictors of stillbirths and neonatal deaths in rural western Uganda. Int J Gynecol Obstet 2016;134(2):190-193. https://doi.org/10.1016/j.ijgo.2016.01.009
28. TBFACTS.ORG. HIV statistics for South Africa – prevalence, incidence, ARVs, deaths. https://www.tbfacts.org/hiv-statistics-south-africa/ (accessed 15 January 2019).
29. Harling G, Moyo S, McGovern ME, et al. National South African HIV prevalence estimates robust despite substantial test non-participation. S Afr Med J 2017;107(7):590-594. https://doi.org/10.7196/SAMJ.2017.v107i7.11207
30. Fowke KR, Nagelkerke NJ, Kimani J, et al. Resistance to HIV-1 infection among persistently seronegative prostitutes in Nairobi, Kenya. Lancet 1996;348(9038):1347-1351. https://doi.org/10.1016/S0140-6736(95)12269-2
31. Pancino G, Saez-Cirion A, Scott-Algara D, Paul P. Natural resistance to HIV infection: Lessons learned from HIV-exposed uninfected individuals. J Infect Dis 2010;202(Suppl 3):S345-S350. https://doi.org/10.1086/655973
32. Lee AC, Katz J, Blencowe H, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. Lancet Glob Health 2013;1(1):e26-e36. https://doi.org/10.1016/S2214-109X(13)70006-8
33. Aiken C. Long-term neurodevelopmental outcomes in small babies. Obstet Gynaecol Reprod Med 2017;27(8):235-238. https://doi.org/10.1016/j.ogrm.2017.06.001
34. Figueras F, Eixarch E, Gratacos E, Gardosi J. Predictiveness of antenatal umbilical artery Doppler for adverse pregnancy outcome in small-for-gestational-age babies according to customised birthweight centiles: Population-based study. BJOG 2008;115(5):590-594. https://doi.org/10.1111/j.1471-0528.2008.01670.x
35. Triunfo S, Crispi F, Gratacos E, Figueras F. Prediction of delivery of small-for-gestational-age neonates and adverse perinatal outcome by fetoplacental Doppler at 37 weeks' gestation. Ultrasound Obstet Gynecol 2017;49(3):364-371. https://doi.org/10.1002/uog.15979
36. Katz J, Lee AC, Kozuki N, et al. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: A pooled country analysis. Lancet 2013;382(9890):417-425. https://doi.org/10.1016/S0140-6736(13)60993-9

Accepted 10 July 2018.

Alcohol 62 (2017) 17–27

Contents lists available at ScienceDirect

Alcohol

journal homepage: http://www.alcoholjournal.org/

A modified Timeline Followback assessment to capture alcohol exposure in pregnant women: Application in the Safe Passage Study

Kimberly Dukes [a, *], Tara Tripp [a], Julie Petersen [a], Fay Robinson [a], Hein Odendaal [b], Amy Elliott [c], Marian Willinger [d], Dale Hereld [e], Cheryl Raffo [a], Hannah C. Kinney [f, g], Coen Groenewald [b], Jyoti Angal [c], Rebecca Young [a], Larry Burd [h], PASS Network

[a] DM-STAT, Inc., One Salem Street, Suite 300, Malden, MA 02148, USA
[b] Stellenbosch University, Department of Obstetrics and Gynecology, Francie van Zijl Avenue, Tygerberg 7505, South Africa
[c] Sanford Research, Center for Health Outcomes and Prevention Research, 2301 E. 60th Street North, Sioux Falls, SD 57104, USA
[d] National Institute of Child Health and Human Development, 31 Center Drive, Building 31, Room 2A32, Bethesda, MD 20892-2425, USA
[e] National Institute on Alcohol Abuse and Alcoholism, 5635 Fishers Lane, Rockville, MD 20852, USA
[f] Boston Children's Hospital, Department of Pathology, 300 Longwood Avenue, Boston, MA 02115, USA
[g] Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA
[h] University of North Dakota, Fetal Alcohol Syndrome Center, School of Medicine & Health Sciences, 501 North Columbia Road, Grand Forks, ND 58203-9037, USA

ARTICLE INFO

Article history:
Received 15 September 2016
Received in revised form
3 February 2017
Accepted 3 February 2017

Keywords:
Timeline followback (TLFB)
Prenatal alcohol exposure
Self-report
Standard drink
Quantity-frequency methods

ABSTRACT

Prenatal alcohol exposure (PAE) has been linked to poor pregnancy outcomes, yet there is no recognized standard for PAE assessment, and the specific effects of quantity, frequency, and timing remain largely unknown. The Safe Passage Study was designed to investigate the role of PAE in a continuum of poor peri- and postnatal outcomes.

The objective of this manuscript is to describe the rationale for, and feasibility of, modifications to the traditional Timeline Followback (TLFB) for collecting PAE information in a large cohort of pregnant women. Participants from the Northern Plains region (in the United States) and Cape Town, South Africa, were followed prospectively using a modified 30-day TLFB interview, administered up to five times, to obtain detailed PAE information. Required modifications for our population included capturing information regarding sharing, type/brand, container size, and duration, in order to accurately record the amount of alcohol consumed. PAE status was defined for 99.9% of the 11,892 enrolled pregnancies at least once during pregnancy and for 92% across all trimesters. Of 53,823 drinks reported, 98% had all items necessary for standard drink computation. Sharing was reported for 74% of drinks in Cape Town, South Africa and for 10% in the Northern Plains. Compared to referent values from the traditional TLFB, 74% and 67% of drinks had different alcohol-by-volume and container size, respectively. Furthermore, a statistically significant difference was found between the number of containers reported and the number of standard drinks computed, using information from the modified TLFB. This is the first study of this size to wholly encompass all of these changes into a single measure in order to more accurately calculate daily consumption and assess patterns over time. The methods used to collect PAE information and create alcohol exposure measures likely increased the accuracy of standard drinks reported and could be generalized to other populations.

Introduction

Prevalence of prenatal alcohol consumption and risk to the fetus

Alcohol use by pregnant women is a significant public health concern in the United States (US) and abroad, despite public-awareness campaigns and product labels warning of threats to

* Corresponding author. DM-STAT, Inc., One Salem Street, Malden, MA 02148, USA. Fax: +1 781 395 4968.
E-mail addresses: Kim.Dukes@dmstat.com, Kim.Dukes@me.com (K. Dukes).

http://dx.doi.org/10.1016/j.alcohol.2017.02.174
0741-8329/

fetal development (Chang, McNamara, Orav, & Wilkins-Haug, 2006). Prenatal alcohol exposure (PAE) has long been linked to neurodevelopmental and growth abnormalities and facial dysmorphology under the rubric of fetal alcohol spectrum disorders (Coriale et al., 2013), the most prevalent and preventable cause of intellectual disability in the US (0.5–9.1/1000) (Burd, Blair, & Dropps, 2012; Viljoen et al., 2005). The prevalence of self-reported PAE in the US between 2006 and 2010 was 8% (Centers for Disease Control and Prevention [CDC], 2012), although higher rates have been reported in American Indians in the Northern Plains (57%) (Iyasu et al., 2002), and in women of mixed ancestry in the Western Cape, South Africa (34%–51%) (May et al., 2000). However, research is limited regarding the impact of PAE early in gestation, specifically the impact to the fetus prior to pregnancy confirmation (Henderson, Gray, & Brocklehurst, 2007; Henderson, Kesmodel, & Gray, 2007; Kesmodel et al., 2012), as well as in the weeks leading up to delivery, when the fetus undergoes rapid growth and neurological development. The specific effects to the fetus of quantity, frequency, and timing (QFT) of PAE remain largely unknown, and conflicting information exists regarding the effects of low-to-moderate levels of exposure (Flak et al., 2014; Henderson, Gray, et al., 2007; Lundsberg, Illuzzi, Belanger, Triche, & Bracken, 2015; Patra et al., 2011).

Methods to obtain PAE

Both biomarkers and self-reported assessment of alcohol consumption are used to determine PAE. *Biomarkers* such as fatty acid ethyl esters, ethyl glucuronide, and ethyl sulfate are objective, do not rely on participant veracity, and are typically obtained through maternal blood, meconium, or cord blood. Many validated *self-reported assessments* of PAE exist, and their appropriateness depends on the end goal of the research. There are brief assessments that screen for alcohol dependence (e.g., Tolerance Annoyance Cut-down Eye-opener, Cut-down Annoyed Guilty Eye-opener, Tolerance Worried Eye-opener Amnesia K[c]ut-down [Chang, 2001]) or that detect "risky" drinking behaviors (e.g., Alcohol Use Disorders Identification Test; Bohn, Babor. & Kranzler, 1995; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). A more lengthy assessment, the Timeline Followback (TLFB), developed by Sobell and Sobell (Sobell, Maisto, Sobell, & Cooper, 1979; Sobell & Sobell, 1979, 1992, 1995), is commonly used to capture the number of self-reported drinks consumed on each day during a reference period (e.g., 30 days), termed "exact recall" (Dawson, 2003). The TLFB is considered one of the most rigorous self-reported exposure assessments in research, valid for recall up to 360 days (Sobell & Sobell, 1992, 1995, 2004). The traditional TLFB includes reference materials defining standard container sizes and alcohol-by-volume (ABV) for four beverage categories (beer, wine, fortified wine, and hard liquor). Prior studies have administered the TLFB interview multiple times antenatally to characterize drinking (e.g., number of standard drinks consumed on average per day) at conception and during pregnancy (Bearer et al., 2003; Jacobson, Chiodo, Sokol, & Jacobson, 2002; Jacobson et al., 2008). A more extensive exact recall method, Form 90, captures additional information on type and size of drinks, but its complexity increases the likelihood of measurement error (Miller, 1996) and its length makes it non-ideal for many research settings.

Agreement between PAE collection methods

There are conflicting reports regarding concordance between biomarkers and self-report in PAE measurement; some studies indicate moderate to substantial agreement (Burd & Hofer, 2008; Himes et al., 2015; Joya et al., 2012; Lange, Shield, Koren, Rehm, & Popova, 2014; Littner, Cudd, O'Riordan, Cwik, & Bearer, 2008; Zelner et al., 2013), and others indicate no agreement (Derauf, Katz, & Easa, 2003). *Limitations of biomarkers* include: 1) lack of coverage throughout pregnancy because results are typically valid for short time windows; 2) specimen sensitivity to collection and storage conditions that may impede extraction of the biomarker result (e.g., necessity to freeze immediately); 3) prohibitive costs and need for specialized technicians and equipment; and 4) lack of generalizability based on willingness to participate (e.g., invasive techniques; Bakhireva & Savage, 2011; Bearer, Stoler, Cook, & Carpenter, 2004),. *Limitations of self-report* include: 1) the majority of studies obtain PAE postpartum, not prospectively throughout pregnancy, potentially yielding inaccurate estimates due to long recall periods (Day, Wagener, & Taylor, 1985; Lange et al., 2014); 2) the collection of self-reported exposure during pregnancy may be biased due to concerns about confidentiality, social stigma (Sobell & Sobell, 2004), or fear the child may be taken away (Bhuvaneswar, Chang, Epstein, & Stern, 2007; Lange et al., 2014); 3) the possibility of inaccurate estimation of quantity consumed, as the participant's interpretation of a "standard" drink may differ from official guidelines (Kerr & Stockwell, 2012; de Visser, 2015); and 4) the complexity and length of assessments such as TLFB and Form 90 are not ideal for many research studies (Miller, 1996). Thus, there is no recognized standard for the assessment of PAE.

Timeline followback feasibility study

Prior to the research described in this report, a feasibility study of 518 women was conducted in the target population, with one objective being to optimize the method with which alcohol exposure information would be ascertained. Non-published findings from the feasibility study indicated that women in our study population commonly reported sharing beverages and often used different container sizes than those referenced in the traditional TLFB. Further, there was a statistically significant difference found between the number of drinks reported in a typical week, solicited from a single question, and the number of standard drinks computed using the traditional TLFB with a 7-day reference period (difference $= -1.24$ drinks, p value $= 0.0254$).

Objective

The Safe Passage Study of the Prenatal Alcohol in Sudden Infant Death Syndrome (SIDS) and Stillbirth (PASS) Network was designed to investigate the role of PAE in a continuum of poor peri- and postnatal outcomes (Dukes et al., 2014). The interviewer-based TLFB was used to capture detailed information regarding QFT of PAE around the time of conception through 1 month post-delivery. The traditional TLFB required modifications for the Safe Passage Study population based on feasibility findings, as well as evidence from the literature showing that for self-report, that what constitutes a standard drink differs from official precepts (Devos-Comby & Lange, 2008). Study investigators modified the standard TLFB to capture information regarding sharing, type/brand of beverages consumed (to assign specific ABV values), and container size, for use in the calculation of standard drinks. Although the modifications were deemed necessary, it was unclear whether it was feasible to obtain this level of detail in a large cohort of pregnant women over several assessment periods. This report describes the modifications made to the standard TLFB used to obtain alcohol exposure data from pregnant women participating in the Safe Passage Study, and highlights our success in obtaining complete and detailed information.

Materials and methods

Study design

The Safe Passage Study enrolled 11,892 unique pregnancies from 10,888 women at high risk for maternal drinking during pregnancy from the Northern Plains region of the US and from Cape Town, South Africa. The maternal-fetal/infant dyad was followed through pregnancy and until 1 year post-delivery. Follow-up was completed on October 4, 2016. The research was overseen by the Network's Steering Committee, an external Advisory and Safety Monitoring Board, and by local institutional review boards and Tribal research councils (Angal, Petersen, Tobacco, & Elliott, 2016; Dukes et al., 2014). At the end of the recruitment visit, each participant was given educational materials on the potential effects of smoking and drinking during pregnancy and was asked if they would like to be referred to local agencies that can help those who would like to reduce their consumption or abstain from using alcohol.

Alcohol exposure assessments

Self-reported alcohol exposure information was collected for the time period around conception, up to four times during pregnancy, and at 1 month post-delivery. Because biomarker analyses were not definitive and were cost prohibitive, the TLFB was chosen as the best method to elicit detailed self-reported alcohol exposure information, and because portions of the populations under study had lower literacy levels, interviewer administration was used. The traditional TLFB collects the number of self-reported standard drinks consumed on each day in a specified time period within four beverage categories (beer, wine, fortified wine, and hard liquor). Reference ABV values and visuals of container sizes are provided for each beverage category. Because women in this population shared beverages and utilized different container sizes than those referenced in the TLFB, as shown in the feasibility study, modifications for our population included collection of each specific beverage consumed, container size (volume), whether sharing was involved, and duration of drinking episode. Collection of these additional details was intended to more accurately assign ABV, reduce inaccuracies resulting from incorrect interpretation of a standard drink, and, in situations with sharing, reduce non-systematic participant estimation regarding the amount individually consumed. In addition, analysis was performed using meconium from 108 infants (72 from South Africa, 36 from Northern Plains), with moderate to substantial agreement between self-report at or after 19 weeks and meconium ethyl glucuronide $\geq$30 ng/g (Cohen's kappa = 0.57) (Himes et al., 2015).

Administration

Each TLFB interviewer received extensive training and completed a proficiency assessment prior to conducting the first interview. On-going trainings and quality assessments were conducted biannually throughout the data collection period (see Supporting Material: Appendix A). In accordance with the traditional TLFB approach, participants were first prompted to consider anchor dates, such as paydays, holidays, other special occasions, and regular events that involved drinking during the 30-day reference period (Sobell & Sobell, 2000). Once all anchor dates were obtained, drinking days were identified, and detailed information was recorded for each unique drinking day, defined to include continued drinking past midnight (Sobell & Sobell, 2004). A modified calendar worksheet and 2D visual prompts (see Supporting Material: Appendix B) aided participants in recall (Sobell & Sobell, 2004). Following the interview, information was transcribed from the calendar worksheet to the TLFB case report form.

Quantity

The traditional Sobell method queries an individual to report the number of standard drinks consumed per day. It has been shown that the amount constituting a standard drink differs from official precepts (Devos-Comby & Lange, 2008). In particular, "beverages whose container or serving sizes are not standard (e.g., 12-oz beer) may pose problems for drinkers when reporting level of alcohol consumption" (Dawson, 2003). The problem is further exacerbated when the participant pours or shares a beverage from a large container, as the volume individually consumed, combined with specific ABV, is often greater than one standard drink. The modifications to the standard TLFB were implemented because it was so crucial in the Safe Passage Study to calculate as accurately as possible the total grams of alcohol consumed for each drinking day, in addition to determining the timing of exposure. Obtaining type/brand of alcohol was important because ABV values vary significantly within each category (e.g., wines 6–18%, beer 4–9%, spirits 16.5–95%). Not accounting for ABV and simply assuming the same ABV for all beverages within a category could result in inaccurate estimates of ethanol consumed, and therefore an under- or over-estimate of the number of standard drinks consumed. Customized lists of alcoholic beverages commonly consumed locally were developed (see Supporting Material: Appendix C) and reflected the fact that beverages consumed in South Africa were different from those in the Northern Plains. This methodology allowed for study of trends in consumption by beverage category and site (Sobell & Sobell, 2004), and has been shown to increase the accuracy of recall (Muggli, Cook, O'Leary, Forster, & Halliday, 2015). Beverage lists were broken into several categories and subcategories: beer, malt liquor, cooler/cider, shooter (mixed shot), cocktail (including packaged, premixed), spirit (including liqueurs and schnapps), and wine (including dessert/fortified), and included over 200 unique codes. If a beverage was not listed or the interviewer was uncertain how to code a beverage, open-text fields were available so entries could be assigned appropriate ABVs prior to data analysis. However, data were reviewed periodically and code lists were updated accordingly to minimize use of open-text fields. Each alcohol code was assigned an ABV value utilizing product labels, government publications, and store and brand websites.[1] Specifying container size, with the use of visual aids and tick marks to indicate fill line, avoided one container being erroneously reported as one standard drink regardless of actual container size and allowed for reports of small quantities (e.g., one sip was recorded as 20 mL). The sharing item was added due to the high prevalence of sharing among certain portions of the study population; however, the participant was prompted to report how much she individually consumed, if known. To accommodate situations of uncertainty, participants were allowed to provide a range of values for number of containers, number of people sharing, and duration of drinking episode. Collection of these values allowed for the use of minimum, maximum, or average values in analyses.

[1] Percent alcohol by volume was derived from multiple sources (e.g., product label, Wegmans.com, Wikipedia.com, http://pubs.niaaa.nih.gov/publications/Tips/tips.htm, Beeradvocate.com, Ratebeer.com, Gooseisland.com, Beer100.com, Missionliquor.com, Drinksmixer.com, Inthespirit.co.uk, About.com) and one ounce is equivalent to 29.57 mL and a weight of 0.79 g/mL. oz., ounces; g, grams; mL, milliliters.

Frequency

Within the 30-day period, repeated drinking patterns (e.g., two 5-oz glasses of Merlot wine every Friday night, with no sharing) were collected only once and applied to each matching day indicated within the TLFB reference period. This approach minimized both interviewer and participant burden, reduced errors in recording, and allowed for examination of typical versus atypical patterns.

Timing

The modified TLFB was administered at the Recruitment Interview (between 6 weeks gestation and delivery), again at up to three prenatal visits (20–24, 28–32, and 34 + weeks), dependent upon timing of enrollment, and at 1 month post-delivery. At the Recruitment Interview, exposure information was collected for the time around conception (15 days before and after last menstrual period [LMP]) and for 30 days prior to the participant's last reported drinking day. At subsequent contacts, if the participant reported consumption since her previous visit, the reference period consisted of the 30 days prior to the last drinking day.

Derived alcohol exposure variables

The number of standard drinks for each beverage reported on a unique drinking day (Fig. 1) was calculated as follows: 1) standardized volumes to ounces (1 mL = 1/29.57 oz.), 2) calculated volume per person ([ounces per container × number of containers] / number of people sharing), 3) calculated grams of ethanol consumed ([volume per person × ABV × (0.79 / 100) × (29.57)], where 0.79 is the specific gravity of ethanol), and 4) calculated number of standard drinks consumed using the US guideline, i.e., 14 g ethanol (National Institute on Alcohol Abuse and Alcoholism, 1998). If a range of values was given for number of containers or number sharing, the mean was used (Brick, 2006). The number of standard drinks for each beverage was summed to provide the total number of standard drinks for that day. Mean drinks per drinking day was calculated as the total number of standard drinks during a period (e.g., week, trimester, pregnancy), divided by the total number of drinking days in that period. Using gestational age (GA), number of standard drinks per day, number of drinking days, and number of days reported in a period, a comprehensive set of variables was created to describe the QFT of alcohol consumption that can be used to define drinking trajectories over the course of pregnancy (Fig. 2).

A conservative approach was employed when calculating quantity and timing of alcohol consumption. Specifically, if ABV could not be determined for a certain beverage, the lowest ABV within the category was assigned. When reference periods overlapped (e.g., last drink was less than 30 days after the previous visit), resulting in duplicate information, data from the shortest recall period were used. This removed the burden of checking for overlap from the interviewer. In the situation where a woman reported drinking, but did not provide quantity information, a value of 0.5 standard drinks was assigned (equivalent to one sip of a 40% ABV spirit) as a conservative approach to prevent exclusion from analyses involving quantity.

Measure	Quantity/Frequency	Timing
Drinking days	Number of drinking days and abstinent days (total and consecutive)	LMP, pregnancy, week, month, trimester
Standard drinks*	Average, maximum, peak BAC, various binge cutoffs (with and without duration)	LMP, pregnancy, day, week, month, trimester, weekends, special occasions

Fig. 2. The array of self-reported alcohol consumption measures collected on the modified Timeline Followback (TLFB). *Countries have differing definitions for what is considered a standard drink. While the US guideline (14 g) was used to define a standard drink in this report, the detail elicited from the modified TLFB allows for derivation based on other national standards. BAC: blood alcohol content; LMP: last menstrual period.

To summarize, information was collected at the drink level for each day of interest (up to five 30-day periods). The drink level data were used to calculate standard drinks for each drinking day, which corresponds to a calendar day and GA. Using this day level data, information was aggregated to time periods of interest, such as ever during pregnancy, week, month, and trimester, as well as any cutoff of interest (e.g., consumption prior to a certain test or assessment). For pregnancies with no drinking reported through the entire pregnancy, every day in the pregnancy was defined as zero standard drinks. Pregnancies enrolled in a later trimester or where drinking was reported at multiple time points do not have drinking information defined for every day in pregnancy.

Statistical methods

To demonstrate the feasibility of using a modified TLFB to collect PAE information in pregnant women enrolled in the Safe Passage Study, data describing the completeness and the quality of the information collected is provided. The results are descriptive in nature and do not include information regarding the number of pregnancies or women exposed or QFT of exposure because it will be reported elsewhere.

Pregnancy level (n = 11,892, reflecting 10,088 participants)

Descriptive statistics, including means, standard deviations (sd), medians, and ranges for continuous variables and frequencies and percentages for nominal variables, are provided by race/ethnicity

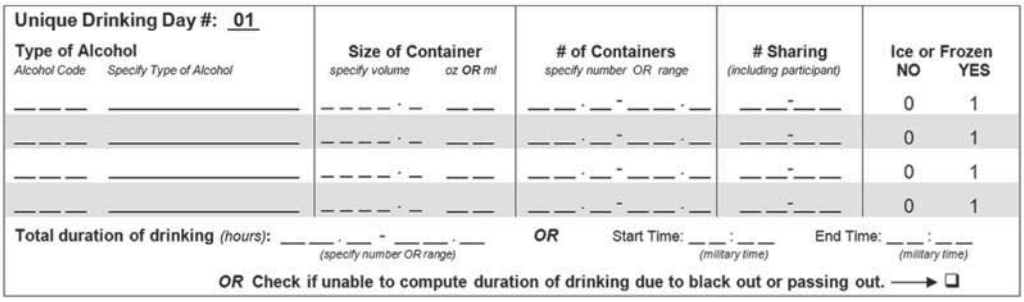

Fig. 1. Excerpt from the Timeline Followback (TLFB) case report form used in the Safe Passage Study to collect drink type, size of container, number of containers, number sharing, ice or frozen, and duration for each unique drinking day in the 30-day reference period.

for selected maternal and infant characteristics. To illustrate the breadth of information collected, descriptive information regarding compliance with visits, TLFB completion rates, and whether QFT could be determined is shown by study visit. Furthermore, information regarding reports of sharing, length of recall (recall period = date of interview minus first day of reference period), inconsistencies in the data, and the determination of PAE status throughout pregnancy is provided. For participants with periods of overlap, we used Cohen's weighted kappa statistic to assess concordance between the numbers of drinking days reported in the overlapping periods: coded as 0, 1, 2, 3, or 4 + days.

Drink level (n = 53,823)

For each beverage category in the modified TLFB, descriptive statistics are provided regarding the number of beverages reported and items required for standard drink calculation (including number missing). Information regarding the items added in the modified TLFB is presented by site for the four beverage categories listed in the traditional TLFB (i.e., beer, wine, fortified wine, and hard liquor/spirits). The proportion of drinks reported with sharing and the proportion with ABV and container sizes differing from TLFB referent values are provided. Reported container sizes are compared descriptively to a wider range of commonly available standard volumes. Information regarding how often participants made use of various options in the data collection process, such as open-text fields and ranges, is also provided.

Validation sample (n = 4309 drinks, n = 1631 pregnancies)

We did not directly ask women to complete both the traditional and the modified TLFB for two reasons: 1) to avoid increased participant burden and 2) the results from the feasibility study strongly suggested the need for modifications. However, a validation sample was developed using reported drinks that 1) did not involve sharing, 2) fell into a "typical" range of standard container sizes (Table 4), and 3) were from the beer, wine, or spirits category. This restricted sample allowed for comparison of the number of containers reported (i.e., number of standard drinks in the traditional TLFB) with the number of standard drinks calculated using the additional information (ABV and container size) from the modified TLFB. The number of containers reported was compared to the number of standard drinks calculated using a paired *t*-test. In addition, using pregnancies from which the drink-level sample was obtained, pregnancy-level analyses, not accounting for re-enrollments, were performed to determine whether classification as a binge drinker was statistically different between the traditional and modified TLFB methods using Cohen's kappa statistics and corresponding 95% confidence intervals.

All analyses were performed using SAS/STAT® version 9.3.[2] *p* values were considered significant if $\alpha < 0.05$, using a two-sided test.

Results

The sample consists of 11,892 pregnancies from 10,088 women in three diverse populations: mixed ancestry (58%) from South Africa, and American Indian (18%) and white (23%) from the Northern Plains (other\not specified [1%]). White women were older, more educated, and had fewer preterm deliveries (<37 weeks gestation) compared to American Indian and mixed ancestry women (Table 1). Mixed ancestry women enrolled later in pregnancy, compared to white and American Indian women. Reference the Safe Passage Study design paper for more information (Dukes et al., 2014).

Of 53,823 drinks reported, beer was the most common, representing over 50%, while cooler/cider, spirit, and wine each represented about 13% (Table 2). All of the items necessary for standard drink computation were completed for over 97% of drinks reported, regardless of beverage category. Missing information was most prevalent for spirits (2.6%), due primarily to missing number sharing and number of containers. Items most likely to be missing were: number of containers for beer, cocktails, cooler/cider, and malt liquor; and number sharing for spirits and wine.

Overall, 10% (n = 5560) of drinks reported made use of the open-text field for type/brand (data not shown). Open-text reports were re-coded to existing codes when possible, or assigned to another ABV, if determinable. As a result, 519 (9.3%) open-text drink reports were coded to the lowest ABV within the corresponding beverage category, and 183 (0.3%) drink reports indicating an unknown beverage type were subsequently assigned to the lowest overall ABV of 2.5%. Overall, 956 (1.8%) drink reports did not have sufficient quantity information provided and were coded to 0.5 standard drinks. Participants opted to provide a range, rather than an exact value, for number of containers and persons sharing in 17% and 9% of drinks, respectively. Of particular note, 47% of all drinks reported involved sharing (74% in South Africa and 10% in the Northern Plains).

Table 3 provides descriptive information regarding items added in the modified TLFB (sharing, ABV, and container size). Across the four categories referenced in the traditional TLFB, at least 66% of drinks reported in South Africa (excluding fortified wine, with few reports) involved sharing, while in the Northern Plains, 21% of spirits and 5% or fewer wine and beer reports involved sharing. Ninety-nine percent and 40% of spirits reported in the Northern Plains and in South Africa, respectively, had an ABV outside the reference range of 43–50%. The majority of wine reports (84% in Northern Plains and 78% in South Africa) had container sizes different from the reference values. In South Africa, almost all (99%) beer reports had container sizes different from the reference. Fig. 3 shows the ABV of spirits reported; for both sites, the majority of drinks fall below the TLFB reference range of 43–50%, primarily due to consumption of liqueurs.

Table 4 compares reported container sizes to a wider range of common container sizes found in the US and South Africa. Excluding shooter, where there are few reports, wine had the largest percentage of 'non-standard' container sizes in the Northern Plains (51.9%), while cocktail had the largest percentage in South Africa (38.2%). Overall, between 6% and 43% of drinks reported, depending on beverage category, were not of sizes commonly available locally.

Ninety-three percent of all eligible visits were completed and the TLFB was successfully collected nearly 100% of the time for participants attending a visit (Table 5). The percentage of pregnancies with complete QF information for all drinks reported was 96.0%, 98.5%, 98.5%, 97.8%, and 98.9% at the recruitment, 20–24 week, 28–32 week, 34 + week, and 1-month postnatal contacts, respectively, while overall, 99% have QF available on any (i.e., some) drinks reported across all visits. Duration of drinking is known for at least 93.9% of pregnancies at each visit. QF was not provided for 1% of women who reported drinking.

All but four pregnancies (missing Recruitment Interview or TLFB) have PAE status defined for at least one trimester of pregnancy (data not shown). PAE status was known for all trimesters in 92% of pregnancies and for every week in 65%. In three hundred and

[2] Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Table 1
Maternal and infant characteristics by race.

	Statistic	South Africa	Northern Plains		Total[c]
		Mixed ancestry n = 6896	American Indian n = 2128	White n = 2755	n = 11,892
Maternal characteristics					
Age (years)	n	6896	2128	2755	11,892
	mean (sd)	24.8 (5.9)	24.8 (5.5)	28.3 (4.9)	25.6 (5.8)
	median	24.0	24.0	28.0	25.0
	(min – max)	(15.0–45.0)	(15.0–43.0)	(16.0–44.0)	(15.0–45.0)
High school educated	n (%)	1683 (24.4%)	1231 (58.0%)	2646 (96.0%)	5652 (47.6%)
Gravidity[a]	n	6870	2030	2698	11,708
	mean (sd)	2.3 (1.3)	3.2 (2.0)	2.5 (1.5)	2.5 (1.5)
	median	2.0	3.0	2.0	2.0
	(min – max)	(1.0–10.0)	(1.0–12.0)	(1.0–14.0)	(1.0–14.0)
Parity[b]	n	6870	2030	2698	11,708
	mean (sd)	1.1 (1.2)	1.8 (1.7)	1.1 (1.1)	1.2 (1.3)
	median	1.0	1.0	1.0	1.0
	(min – max)	(0.0–8.0)	(0.0–10.0)	(0.0–9.0)	(0.0–10.0)
Gestational age at enrollment (weeks)	n	6896	2128	2755	11,892
	mean (sd)	20.1 (7.1)	16.3 (7.1)	16.0 (3.3)	18.5 (6.7)
	median	20.0	15.0	16.1	17.4
	(min – max)	(6.0–40.3)	(3.6–39.6)	(5.0–35.6)	(3.6–40.3)
Infant characteristics					
Preterm delivery (<37 weeks)	n (%)	1053 (15.2%)	296 (14.8%)	272 (10.0%)	1634 (13.9%)
Birth weight (grams)	n	6806	1809	2680	11,395
	mean (sd)	2964.6 (617.3)	3409.6 (649.5)	3385.4 (601.3)	3135.7 (655.0)
	median	3000.0	3447.0	3430.0	3170.0
	(min – max)	(50.0–5740.0)	(170.0–5925.0)	(43.0–5690.0)	(43.0–5925.0)

[a] Gravidity = Number of times a woman has been pregnant including index pregnancy.
[b] Parity = Number of >20 week births (viable and non-viable) excluding index pregnancy. Multiples count as one birth.
[c] Includes women with other and missing race.

sixty-one (3.7%) pregnancies the quantity of a sip was reported at least once and, of these, 30 (0.3%) reported only sips of (mostly communion) wine and could be classified as not drinking. The average post-recruitment recall period for the TLFB, when drinking was reported, was 44.3 ± 19.2 days. The percentage of pregnancies with some overlap in days reported at different visits was 9.8%, with an average of 23.1 ± 33.4 days of overlap. Of 1325 reporting periods (3% of 43,571) with at least one overlapping day, the

Table 2
Drink level Timeline Followback (TLFB) collection information.

Beverage category	Number reported [a]	Able to calculate number of standard drinks	Information missing for calculation of standard drinks [b]		Unknown type/brand (assigned lowest ABV)	Number with sharing
Beer	27,232 (50.6%)	26,784 (98.4%)	n Container size Number of containers Number sharing	448 38 (8.5%) 313 (69.9%) 270 (60.3%)	NA	16,141 (59.3%)
Cocktail	3436 (6.4%)	3397 (98.9%)	n Container size Number of containers Number sharing	39 21 (53.9)% 22 (56.4)% 9 (23.1%)	175 (5.1%)	407 (11.9%)
Cooler/Cider	6757 (12.6%)	6656 (98.5%)	n Container size Number of containers Number sharing	101 9 (8.9%) 75 (74.3%) 37 (36.6%)	14 (0.2%)	2775 (41.1%)
Malt Liquor	2108 (3.9%)	2094 (99.3%)	n Container size Number of containers Number sharing	14 2 (14.3%) 8 (57.1%) 6 (42.9%)	49 (2.3%)	553 (26.2%)
Shooter (Mixed Shot)	341 (0.6%)	340 (99.7%)	n Container size Number of containers Number sharing	NA NA NA NA	110 (32.3%)	9 (2.6%)
Spirit	6990 (13.0%)	6807 (97.4%)	n Container size Number of containers Number sharing	183 74 (40.4%) 118 (64.5%) 157 (85.8%)	171 (2.5%)	3239 (46.3%)
Wine	6776 (12.6%)	6711 (99.0%)	n Container size Number of containers Number sharing	65 10 (15.4%) 26 (40.0%) 53 (81.5%)	NA	1893 (27.9%)

[a] There were 183 (0.3%) unknown drink reports.
[b] These drink reports will be assigned a value of 0.5 standard drinks.

Table 3
Items added in the modified Timeline Followback (TLFB) compared to traditional TLFB reference values by site (NP: Northern Plains, SA: South Africa).

Categories referenced in TLFB	Drinks reported		Statistic	Reported drinks with sharing involved		ABV referenced in TLFB	Reported drinks with different ABV [c]		Container size referenced in TLFB	Reported drinks with different container size	
	NP	SA		NP	SA		NP	SA		NP	SA
Beer (n = 27,232)	9330	17,902	n (%)	469 (5.0%)	15,672 (87.5%)	5%	6672 (71.5%)	14,927 (83.4%)	12 oz	1643 (17.6%) [d]	17,656 (98.6%) [d]
			mean (sd)	NA	NA		4.3 (0.4)	5.4 (0.3)	340 mL		
Wine (n = 6523)	3920	2603	n (%)	127 (3.2%)	1728 (66.4%)	10-12%	2949 (75.2%)	1208 (46.4%)	5, 25, 40 oz	3304 (84.3%) [d]	2027 (77.9%) [d]
			mean (sd)	NA	NA		12.6 (1.0)	11.2 (2.4)	150, 750, 1500 mL		
Fortified Wine[a] (n = 253)	43	210	n (%)	3 (7.0%)	35 (16.7%)	16-18%	0 (0.0%) NA	113 (53.8%)	3, 25 oz	39 (90.7%) [d]	170 (81.0%) [d]
			mean (sd)	NA	NA			12.5 (0.0)	100, 750 mL		
Spirit[b] (n = 6990)	3115	3875	n (%)	658 (21.1%)	2581 (66.6%)	43-50%	3080 (98.9%)	1548 (39.9%)	1.5, 12, 26, 40 oz	1590 (51.0%) [d]	977 (25.2%) [d]
			mean (sd)	NA	NA		36.2 (6.8)	27.1 (9.9)	50, 340, 750, 1000 mL		

[a] Fortified wine is captured as a sub-category of wine in the modified TLFB and includes dessert wines.
[b] Equivalent to the hard liquor reference in the traditional TLFB.
[c] Means and standard deviations are all reported in ounces.
[d] See Table 4 for further details.

weighted Cohen's kappa comparing number of drinking days reported was 0.4267 (95% CI: 0.3803, 0.4732), indicating moderate agreement (data not shown). Furthermore, in 71% of discordant cases, the later report indicated less drinking than the report with shorter recall; most often, the later report indicated no drinking vs. some drinking reported earlier.

Validation sample (4309 drinks, 1631 pregnancies)

In the Northern Plains, the number of standard drinks computed using the modified TLFB was statistically significantly higher (all p values < 0.0001) than the number of containers reported for the beer (mean ± std deviation) (1.0 ± 1.8), spirit (4.4 ± 6.1), and wine

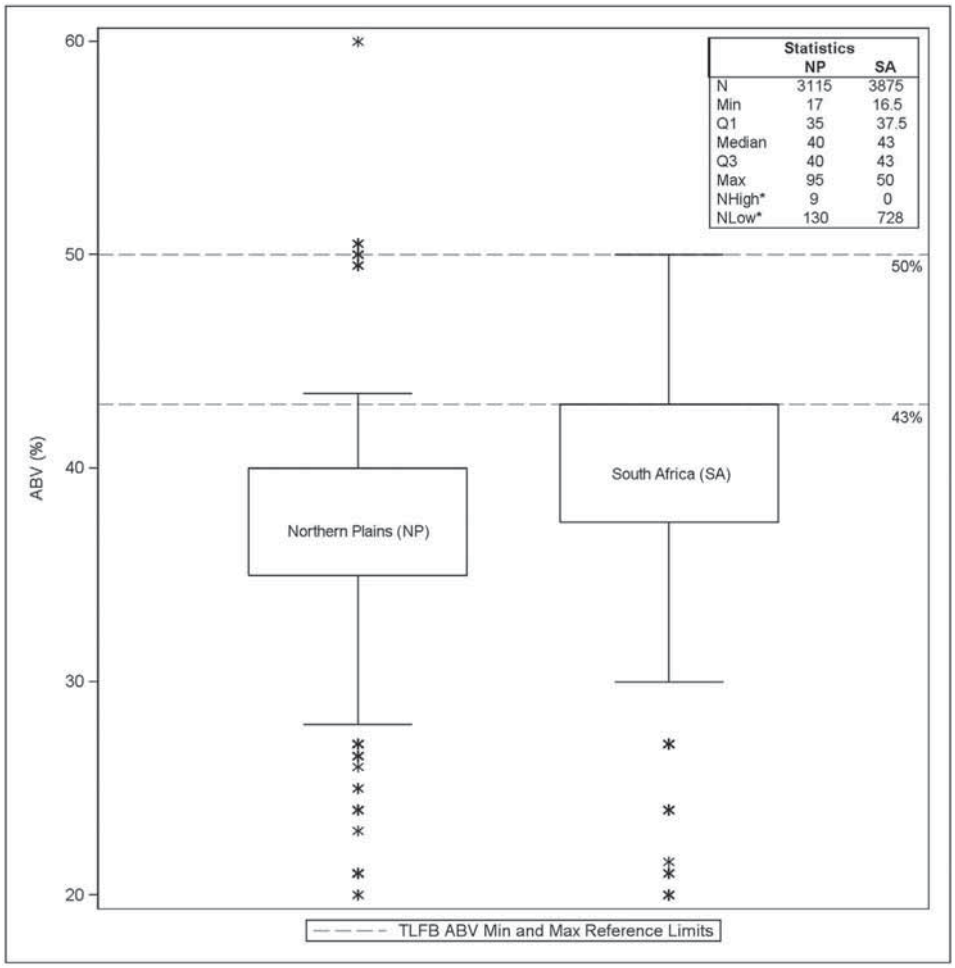

Fig. 3. A boxplot of spirit ABV (%) by site representing the minimum, first quartile, median, third quartile, and maximum. NHigh and NLow refer to the number of drink reports clipped from the visual plot where ABV >60% or <20%, respectively. ABV: Alcohol by Volume.

Table 4
Comparison to common container sizes by site (NP: Northern Plains, SA: South Africa).

Beverage category	Drinks reported		Statistic	Standard[a] container sizes	Drinks with non-standard[a] container size		
	NP	SA			NP	SA	Overall
Beer	9330	17,902	n (%)	12, 16, 22, 40, 64 oz 330, 340, 440, 650, 660, 750 mL	713 (7.6%)	1025 (5.7%)	1738 (6.4%)
Cocktail	3085	351	n (%)	4, 6, 8, 12, 16 oz 100, 150, 200, 250 mL	976 (31.6%)	134 (38.2%)	1110 (32.3%)
Cooler/Cider	317	6440	n (%)	12 oz 275, 300, 330, 340, 660, 750, 3000 mL	103 (32.5%)	463 (7.2%)	566 (8.4%)
Malt Liquor	2108	0	n (%)	8, 9, 12, 16, 22, 40 oz 330, 750 mL	899 (42.6%)	0 (0.0%)	899 (42.6%)
Shooter (Mixed Shot)	286	55	n (%)	1, 1.5, 2 oz 25, 50 mL	22 (7.7%)	41 (74.5%)	63 (18.5%)
Spirit	3115	3875	n (%)	1, 1.5, 12, 16, 25, 26, 40, 59 oz 20, 50, 100, 150, 200, 340, 375, 750, 1000, 1750 mL	1089 (35.0%)	330 (8.5%)	1419 (20.3%)
Wine	3963	2813	n (%)	3, 5, 6, 9, 25, 40 oz 100, 150, 250, 330, 340, 375, 660, 750, 1000, 1500, 2000, 3000, 5000 mL	2057 (51.9%)	466 (16.6%)	2523 (37.2%)

[a] Standard container sizes are equitable to common container sizes found in the study locations.

Table 5
Participant level Timeline Followback (TLFB) collection information.

Visit	Contact complete[a]	TLFB completed	Timing determined	Quantity/frequency available		Duration available	
				Any	All	Any	All
Recruitment	11,886/11,892 (99.9%)	11,886/11,886 (100.0%)	99.7%	99.0%	96.0%	97.3%	94.0%
20–24 weeks	8444/9221 (91.6%)	8429/8444 (99.8%)	100%	99.3%	98.5%	96.6%	94.1%
28–32 weeks	3339/3531 (94.6%)	3338/3339 (99.9%)	100%	99.3%	98.5%	95.8%	93.9%
34+ weeks	10,139/10,713 (94.6%)	10,119/10,139 (99.8%)	100%	99.2%	97.8%	95.8%	94.8%
1 month	9494/11,365 (83.5%)	9446/9494 (99.5%)	100%	99.2%	98.9%	96.4%	95.3%
All	43,302/46,722 (92.7%)	43,218/43,302 (99.8%)	99.8%	99.0%	96.8%	96.9%	94.3%

[a] Depending on the time of enrollment, not all participants are eligible for all prenatal visits.

(0.9 ± 0.9) categories (Table 6). At the pregnancy level, 32.2% were classified as binge drinkers (four or more drinks on an occasion), based upon data from the modified TLFB, vs. 23.3% based upon the traditional TLFB (data not shown). In South Africa, a smaller proportion of pregnancies were available for this analysis (7.5%) as compared to the Northern Plains (22.4%), due to the high proportion of sharing in South Africa. The number of standard drinks calculated was statistically significantly higher (all p values < 0.0015) using the modified as compared to the traditional TLFB for the beer, spirits, and wine categories in South Africa; however, the magnitude of the differences were not as great as those reported in the Northern Plains (Table 6).

Discussion

Summary

While other studies have adapted alcohol exposure assessments to collect type/brand, container size, and sharing information (Dawson, 2003; Day et al., 1985; Kaskutas & Graves, 2001; Kaskutas

Table 6
Comparison of standard drinks as calculated by modified and traditional Timeline Followback (TLFB).

	n	Statistic	Modified TLFB	Traditional TLFB	Difference (Modified-Traditional)	p value
Northern Plains						
Beer	961	mean (sd) (min – max)	4.6 (4.3) (0.5–48.1)	3.6 (2.9) (0.5–24.0)	1.0 (1.8) (−5.0 to 24.1)	<0.0001
Spirit	582	mean (sd) (min – max)	7.2 (7.6) (0.5–39.6)	2.8 (1.8) (1.0–12.0)	4.4 (6.1) (−2.3 to 34.6)	<0.0001
Wine	1992	mean (sd) (min – max)	2.4 (1.6) (0.4–30.0)	1.5 (0.9) (0.3–15.0)	0.9 (0.9) (−0.8 to 15.0)	<0.0001
South Africa						
Beer	109	mean (sd) (min – max)	3.9 (3.0) (0.9–15.5)	3.5 (2.6) (1.0–12.0)	0.4 (0.7) (−0.6 to 5.5)	<0.0001
Spirit	342	mean (sd) (min – max)	4.2 (6.2) (0.5–81.9)	2.9 (2.3) (1.0–22.5)	1.3 (4.6) (−4.2 to 59.4)	<0.0001
Wine	307	mean (sd) (min – max)	2.8 (3.3) (0.6–37.4)	2.6 (2.5) (1.0–26.5)	0.3 (1.4) (−2.2 to 13.3)	0.0015

& Kerr, 2008; Muggli et al., 2015), this is the first study of this size to wholly encompass all of these changes into a single measure in order to more accurately calculate daily consumption and assess patterns over time.

Modifications to the standard TLFB and associated aids (e.g., modified calendar worksheets, pictures of drinking containers), as well as on-going interviewer trainings and data monitoring checks, were required for our study to aid participant recall, ensure uniformity of collection, and limit missing information. Of primary concern was whether collecting this level of detail for each beverage consumed for each day in a 30-day recall period would be feasible in high-risk pregnant women in the Northern Plains, US and the Western Cape of South Africa, given the transience of the populations and the sensitivity of the research topic. An additional concern was that the study protocol required exposure information to be collected at up to four assessment periods during pregnancy and one assessment post pregnancy, whereas most studies of rare pregnancy outcomes, such as stillbirth and SIDS, typically collect PAE only once during the postpartum period (Bailey & Sokol, 2011; Henderson, Gray, et al., 2007; Iyasu et al., 2002).

We were able to successfully capture the additional information required for standard drink computation using the modified TLFB in 11,892 pregnancies from Safe Passage Study participants. Specifically, PAE status was defined for 99.9% of pregnancies at least once during pregnancy and was defined for all three trimesters in 92%, with complete QFT obtained for 98.2% (52,867/53,823) of all drinks reported.

Further, the modified TLFB likely provides a more accurate assessment of PAE as compared to the traditional TLFB, based on the results of our 2007 feasibility study, where we found that women tended to report consuming less when asked simply to report the number of standard drinks in a period vs. completing the traditional TLFB method, as well as our validation study where we showed statistically significant under-reporting of standard drinks when comparing the traditional vs. the modified TLFB methods (e.g., 3.2 fewer spirit standard drinks, on average). The need for the modifications is further supported by the following results: 1) approximately 47% of all drinks reported included sharing (74% in South Africa and 10% in the Northern Plains); 2) compared to the referent values provided with the traditional TLFB, 74.4% and 66.8% of drinks reported had different ABV and container size, respectively; 3) between 6% and 43% of drink reports, depending on beverage category, differed from container sizes commonly utilized at the study locations; and 4) 17% and 9% of drinks reported included a range (instead of a single value) for the number of containers and persons sharing, respectively.

Our findings provide unique insight into how often women would be making an interpretation to convert individual consumption to standard drinks, which can result in both under- and over-reporting, and corroborate findings from other studies (Devos-Comby & Lange, 2008) with respect to obtaining more precise estimates of standard drinks when exact ABV, container size, and sharing are incorporated. The most common container size for a glass of wine reported in the Northern Plains was 6 oz. (23.8%), while the TLFB referent size is 5 oz. (14.0%). Some restaurants also offer larger 9-oz. pours (2.1% reported), which may still be interpreted by a participant as one "drink" using the traditional TLFB approach. Comparing these container sizes and assuming 12% ABV, one 5-oz glass of wine is equivalent to one standard drink, while a 6-oz and 9-oz glass are equivalent to 1.2 and 1.8 standard drinks, respectively (Table 7). This difference in how container size with a fixed ABV equates to the number of standard drinks increases as the number of glasses consumed increases. Similarly, the potency of ethanol, or ABV, in a beverage greatly affects the number of standard drinks computed. This is most evident for spirits, where ABVs reported in our study ranged from 16.5% to 95%. Among the 7025 spirits reported, 60% in the Northern Plains and only 1.1% in South Africa had an ABV that fell within the referent range of 43–50%; without capturing specific type/brand of alcohol, these reports would have represented over-estimates of consumption.

Table 7
Standard drinks computed from various wine pours.

Reference ABV 12%		
Container size	Number of containers	Standard drinks computed
5 oz	1	1
	2	2
	4	4
6 oz	1	1.2
	2	2.4
	4	4.8
9 oz	1	1.8
	2	3.6
	4	7.2

Considerations

Some factors considered during the planning and execution phase for the collection of PAE in the Safe Passage Study are briefly discussed below.

Under-reporting

Customized tools were developed to aid recall (e.g., modified calendar worksheets, customized 2D visual aids for container sizes, site-specific alcohol code lists; Muggli et al., 2015; Sobell & Sobell, 2004). Efforts were made to reduce under-reporting due to social stigma or fear the child may be taken away from the participant. At study onset, a Certificate of Confidentiality was established to protect participants in select US sites. Further, study staff were often from the same community as the participant, and rapport was built over the course of pregnancy. We believe that under-reporting was minimized based on women reporting sips of alcohol in our study, likely indicative of truthfulness and a strong sense of trust between the participants and study staff. A validation study (Himes et al., 2015) using a subset of Safe Passage Study women (n = 108, case-control design), indicated strong concordance between maternal report and meconium biomarkers.

Cocktails and mixed shots/shooters

ABVs and volumes for cocktails and mixed shots/shooters vary widely, and drinks in this category are not always mixed using the same parts or ingredients, even when consumed in a bar or restaurant setting (Kerr, Patterson, Koenen, & Greenfield, 2008). To simplify the collection of standard drink information for research, it has typically been assumed that a cocktail contains a single shot (1.5 oz.) of spirits with a standard ABV of 40%. In our study, however, the interviewer prompted women to provide specific information regarding container size, contents, and how the drink was mixed. When known, only alcoholic contents were recorded; otherwise, the reported container size and the specific ABV for the mixed beverage were used in the computation of standard drinks, as described in the Methods section.

Limitations

While we believe that our study data are comprehensive and provide additional accuracy over the standard TLFB, there were

limitations in this application of the modified method. First, as in the traditional TLFB, it was necessary to make assumptions to uniformly assign ABV for certain drinks, notably cocktails (6.4% of drinks reported), where the specific ingredients were not listed separately. However, given the level of detail reported, we believe our calculations were more accurate than would have been obtained using the traditional method. Second, it has been reported that the TLFB may not be well suited for situations where researchers are attempting to generalize exposure patterns across time for participants who have infrequent or inconsistent drinking (Dawson, 2003). These concerns were minimized by the implementation of multiple collection time points throughout pregnancy and postpartum to reflect exposure during each trimester. Lastly, it is important to note that the modified TLFB does require extensive resources (e.g., to become familiar with local beverages and practices). However, we felt the benefit of obtaining the additional information was necessary to address our research question and outweighed the associated costs.

Conclusion

In a cohort of 11,892 pregnancies in 10,088 women from the Safe Passage Study, over multiple assessment periods, we successfully captured complete and detailed PAE information, the success of which will be advantageous toward addressing the study's primary analytic goals. The additional information required for the modified TLFB included type/brand of alcohol, whether sharing occurred, container size, and duration of drinking, as well as the use of codes with specific ABV assignment. The modifications likely increased the accuracy of standard drink computation and reduced nonsystematic misclassification of exposure. In addition, though not demonstrated explicitly in this manuscript, the addition of duration will allow researchers to assess measures of exposure not available using the traditional TLFB (e.g., blood alcohol concentrations and definitions of binge that account for duration). Given our success, we think the modified approach has applications in other settings where detailed QFT information is necessary.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Indian Health Service (IHS).

Glossary

Timeline Followback (TLFB) Interview (Alcohol): The Alcohol TLFB Interview is a drinking assessment method that obtains estimates of the quantity of daily drinking and has been evaluated with clinical and nonclinical populations.

Western Cape, South Africa: A province of South Africa, situated in the southwestern part of the country.

Acknowledgments

The authors gratefully acknowledge the cooperation of the study participants, PASS investigators and members of the NICHD Advisory and Safety Monitoring Board: Elizabeth Thom, PhD (Chair); The Reverend Phillip Cato, PhD; James W. Collins, Jr., MD, MPH; Terry Dwyer, MD, MPH; George Macones, MD; Philip A. May, PhD; Richard M. Pauli, MD, PhD; Raymond W. Redline, MD; and Michael Varner, MD. The authors gratefully acknowledge Sandra and Joseph Jacobson for sharing their expertise with the timeline followback method in the pilot project that preceded the Safe Passage Study. The PASS Research Network is supported by the National Institute on Alcohol Abuse and Alcoholism, Eunice Kennedy Shriver National Institute of Child Health and Human Development, and National Institute on Deafness and Other Communication Disorders through the Cooperative Agreement Mechanism (U01 HD055154, U01 HD045935, U01 HD055155, U01 HD045991, and U01 AA016501). The following institutions and researchers comprise the PASS Network (additional network members other than authors listed):

DCAC: Data Management/Information Technology: Travis Baker, BS.

DBPC: *Assistant Director*: Robin L. Haynes, PhD; *Co-investigators*: David S. Paterson, PhD, Kevin G. Broadbelt, PhD, Kyriacos Markianos, PhD, Ingrid A. Holm, MD, Theonia Boyd, MD, Drucilla Roberts, MD, Richard G. Goldstein, MD, Hanno Stein, PhD; *Technicians*: Claire Maggiotto, BS, Catherine Hassett, BS, Kathryn Schissler, BS.

CCS Northern Plains: *Co-investigators*: Donald Habbe, MD, H. Eugene Hoyme, MD, Bradley Randall, MD, Mary Ann Sens, MD, PhD, Peter Van Eerden, MD; *Project Management*: Elizabeth Berg, RN, Christa Friedrich, MS, Marge Jackson, BA, Luke Mack, MA, Liz Swenson, RN, Deb Tobacco, MA.

CCS South Africa: *Co-investigator and Project Manager*: Coen Groenewald, MBChB, MMed, FCOG environmental, M Comm; *Project Management*: Erna Carstens, RN, Mandy Potter, RN, Lucy Brink, MSc, Carlie du Plessis, RN, Milly de Jager RN.

PAC: *Project Management:* J. David Nugent, MA, Carmen Condon, BA; *Data Analysis*: Joseph R. Isler, PhD, Margaret C. Shair, BA, Tracy Thai, MA, Joel S. Yang, PhD.

NIH: *Project Scientists*: Howard J. Hoffman, PhD (NIDCD), Chuan-Ming Li, MD, PhD (NIDCD); *Program Officers*: Bill Dunty, PhD (NIAAA), Tonse Raju, MD, DCH (NICHD), Gordon B. Hughes, MD (NIDCD).

Further, the following individuals made significant contributions to the research and warrant recognition:

DCAC: Idania Ramirez, MPH, Jamie Collins, PhD, Laura Spurchise, MPH, Derek Petersen, BS.

DBPC: Richard A. Belliveau, BA, Kristin McMillan, BA, Megan Minter, MS.

PAC: Johnston T. Grier, BA, Emilia F. Vignola, BA, Joseph J. Violaris, BA.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.alcohol.2017.02.174.

References

Angal, J., Petersen, J. M., Tobacco, D., & Elliott, A. J. (2016). Ethics review for a multisite project involving Tribal Nations in the Northern Plains. *Journal of Empirical Research on Human Research Ethics, 11*, 91–96. http://dx.doi.org/10.1177/1556264616631657. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/26928897/.

Bailey, B. A., & Sokol, R. J. (2011). Prenatal alcohol exposure and miscarriage, stillbirth, preterm delivery, and sudden infant death syndrome. *Alcohol Research & Health, 34*, 86–91.

Bakhireva, L. N., & Savage, D. D. (2011). Focus on: Biomarkers of fetal alcohol exposure and fetal alcohol effects. *Alcohol Research & Health, 34*, 56–63.

Bearer, C. F., Jacobson, J. L., Jacobson, S. W., Barr, D., Croxford, J., Molteno, C. D., et al. (2003). Validation of a new biomarker of fetal exposure to alcohol. *The Journal of Pediatrics, 143*, 463–469. http://dx.doi.org/10.1067/S0022-3476(03)00442-6.

Bearer, C. F., Stoler, J. M., Cook, J. D., & Carpenter, S. J. (2004). Biomarkers of alcohol use in pregnancy. *Alcohol Research & Health, 28*, 38–43.

Bhuvaneswar, C. G., Chang, G., Epstein, L. A., & Stern, T. A. (2007). Alcohol use during pregnancy: Prevalence and impact. *Primary Care Companion to the Journal of Clinical Psychiatry, 9*, 455–460.

Bohn, M. J., Babor, T. F., & Kranzler, H. R. (1995). The Alcohol Use Disorders Identification Test (AUDIT): Validation of a screening instrument for use in medical settings. *Journal of Studies on Alcohol, 56*, 423–432.

Brick, J. (2006). Standardization of alcohol calculations in research. *Alcoholism: Clinical and Experimental Research, 30*, 1276–1287. http://dx.doi.org/10.1111/j.1530-0277.2006.00155.x.

Burd, L., Blair, J., & Dropps, K. (2012). Prenatal alcohol exposure, blood alcohol concentrations and alcohol elimination rates for the mother, fetus and newborn. *Journal of Perinatology, 32*, 652–659. http://dx.doi.org/10.1038/jp.2012.57.

Burd, L., & Hofer, R. (2008). Biomarkers for detection of prenatal alcohol exposure: A critical review of fatty acid ethyl esters in meconium. *Birth Defects Research. Part A, Clinical and Molecular Teratology, 82*, 487–493. http://dx.doi.org/10.1002/bdra.20464.

Centers for Disease Control and Prevention (CDC). (2012). Alcohol use and binge drinking among women of childbearing age—United States, 2006–2010. *MMWR Morbidity and Mortality Weekly Report, 61*, 534–538.

Chang, G. (2001). Alcohol-screening instruments for pregnant women. *Alcohol Research & Health, 25*, 204–209.

Chang, G., McNamara, T. K., Orav, E. J., & Wilkins-Haug, L. (2006). Alcohol use by pregnant women: Partners, knowledge, and other predictors. *Journal of Studies on Alcohol, 67*, 245–251.

Coriale, G., Fiorentino, D., Di Lauro, F., Marchitelli, R., Scalese, B., Fiore, M., et al. (2013). Fetal alcohol spectrum disorder (FASD): Neurobehavioral profile, indications for diagnosis and treatment. *Rivista di Psichiatria, 48*, 359–369. http://dx.doi.org/10.1708/1356.15062.

Dawson, D. A. (2003). Methodological issues in measuring alcohol use. *Alcohol Research & Health, 27*, 18–29.

Day, N. L., Wagener, D. K., & Taylor, P. M. (1985). Measurement of substance use during pregnancy: Methodologic issues. *NIDA Research Monograph, 59*, 36–47.

Derauf, C., Katz, A. R., & Easa, D. (2003). Agreement between maternal self-reported ethanol intake and tobacco use during pregnancy and meconium assays for fatty acid ethyl esters and cotinine. *American Journal of Epidemiology, 158*, 705–709.

Devos-Comby, L., & Lange, J. E. (2008). "My drink is larger than yours"? A literature review of self-defined drink sizes and standard drinks. *Current Drug Abuse Reviews, 1*, 162–176.

Dukes, K. A., Burd, L., Elliott, A. J., Fifer, W. P., Folkerth, R. D., Hankins, G. D., et al. (2014). The safe passage study: Design, methods, recruitment, and follow-up approach. *Paediatric and Perinatal Epidemiology, 28*, 455–465. http://dx.doi.org/10.1111/ppe.12136.

Flak, A. L., Su, S., Bertrand, J., Denny, C. H., Kesmodel, U. S., & Cogswell, M. E. (2014). The association of mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: A meta-analysis. *Alcoholism: Clinical and Experimental Research, 38*, 214–226. http://dx.doi.org/10.1111/acer.12214.

Henderson, J., Gray, R., & Brocklehurst, P. (2007). Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome. *BJOG British Journal of Obstetrics and Gynaecology, 114*, 243–252. http://dx.doi.org/10.1111/j.1471-0528.2006.01163.x.

Henderson, J., Kesmodel, U., & Gray, R. (2007). Systematic review of the fetal effects of prenatal binge-drinking. *Journal of Epidemiology and Community Health, 61*, 1069–1073. http://dx.doi.org/10.1136/jech.2006.054213.

Himes, S. K., Dukes, K. A., Tripp, T., Petersen, J. M., Raffo, C., Burd, L., et al. (2015). Clinical sensitivity and specificity of meconium fatty acid ethyl ester, ethyl glucuronide, and ethyl sulfate for detecting maternal drinking during pregnancy. *Clinical Chemistry, 61*, 523–532. http://dx.doi.org/10.1373/clinchem.2014.233718.

Iyasu, S., Randall, L. L., Welty, T. K., Hsia, J., Kinney, H. C., Mandell, F., et al. (2002). Risk factors for sudden infant death syndrome among northern plains Indians. *JAMA The Journal of the American Medical Association, 288*, 2717–2723.

Jacobson, S. W., Chiodo, L. M., Sokol, R. J., & Jacobson, J. L. (2002). Validity of maternal report of prenatal alcohol, cocaine, and smoking in relation to neurobehavioral outcome. *Pediatrics, 109*, 815–825.

Jacobson, S. W., Stanton, M. E., Molteno, C. D., Burden, M. J., Fuller, D. S., Hoyme, H. E., et al. (2008). Impaired eyeblink conditioning in children with fetal alcohol syndrome. *Alcoholism: Clinical and Experimental Research, 32*, 365–372. http://dx.doi.org/10.1111/j.1530-0277.2007.00585.x.

Joya, X., Friguls, B., Ortigosa, S., Papaseit, E., Martinez, S. E., Manich, A., et al. (2012). Determination of maternal-fetal biomarkers of prenatal exposure to ethanol: A review. *Journal of Pharmaceutical and Biomedical Analysis, 69*, 209–222. http://dx.doi.org/10.1016/j.jpba.2012.01.006.

Kaskutas, L. A., & Graves, K. (2001). Pre-pregnancy drinking: How drink size affects risk assessment. *Addiction, 96*, 1199–1209. http://dx.doi.org/10.1080/09652140120060789.

Kaskutas, L. A., & Kerr, W. C. (2008). Accuracy of photographs to capture respondent-defined drink size. *Journal of Studies on Alcohol and Drugs, 69*, 605–610.

Kerr, W. C., Patterson, D., Koenen, M. A., & Greenfield, T. K. (2008). Alcohol content variation of bar and restaurant drinks in Northern California. *Alcoholism: Clinical and Experimental Research, 32*, 1623–1629. http://dx.doi.org/10.1111/j.1530-0277.2008.00741.x.

Kerr, W. C., & Stockwell, T. (2012). Understanding standard drinks and drinking guidelines. *Drug and Alcohol Review, 31*, 200–205. http://dx.doi.org/10.1111/j.1465-3362.2011.00374.x.

Kesmodel, U. S., Bertrand, J., Støvring, H., Skarpness, B., Denny, C. H., & Mortensen, E. L. (2012). The effect of different alcohol drinking patterns in early to mid pregnancy on the child's intelligence, attention, and executive function. *BJOG British Journal of Obstetrics and Gynaecology, 119*, 1180–1190. http://dx.doi.org/10.1111/j.1471-0528.2012.03393.x.

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 Childbirth, 14*, 127. http://dx.doi.org/10.1186/1471-2393-14-127.

Littner, Y., Cudd, T. A., O'Riordan, M. A., Cwik, A., & Bearer, C. F. (2008). Elevated fatty acid ethyl esters in meconium of sheep fetuses exposed in utero to ethanol—a new animal model. *Pediatric Research, 63*, 164–168. http://dx.doi.org/10.1203/PDR.0b013e31815f651e.

Lundsberg, L. S., Illuzzi, J. L., Belanger, K., Triche, E. W., & Bracken, M. B. (2015). Low-to-moderate prenatal alcohol consumption and the risk of selected birth outcomes: A prospective cohort study. *Annals of Epidemiology, 25*, 46–54. http://dx.doi.org/10.1016/j.annepidem.2014.10.011. e43.

May, P. A., Brooke, L., Gossage, J. P., Croxford, J., Adnams, C., Jones, K. L., et al. (2000). Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape province. *American Journal of Public Health, 90*, 1905–1912.

Miller, W. R. (1996). *Form 90: A structured assessment interview for drinking and related behaviors test manual*. Rockville, MD: National Institutes of Health.

Muggli, E., Cook, B., O'Leary, C., Forster, D., & Halliday, J. (2015). Increasing accurate self-report in surveys of pregnancy alcohol use. *Midwifery, 31*, e23–28. http://dx.doi.org/10.1016/j.midw.2014.11.003.

National Institute on Alcohol Abuse and Alcoholism. (1998). *What is a standard drink?*. Washington, DC https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/what-standard-drink.

Patra, J., Bakker, R., Irving, H., Jaddoe, V. W., Malini, S., & Rehm, J. (2011). Dose-response relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA) – a systematic review and meta-analyses. *BJOG British Journal of Obstetrics and Gynaecology, 118*, 1411–1421. http://dx.doi.org/10.1111/j.1471-0528.2011.03050.x.

Saunders, J. B., Aasland, O. G., Babor, T. F., de la Fuente, J. R., & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption–II. *Addiction, 88*, 791–804.

Sobell, L. C., Maisto, S. A., Sobell, M. B., & Cooper, A. M. (1979). Reliability of alcohol abusers' self-reports of drinking behavior. *Behaviour Research and Therapy, 17*, 157–160.

Sobell, L. C., & Sobell, M. B. (1979). *Alcohol timeline followback instructional training video*. Toronto: Canada Addiction Research Foundation.

Sobell, L. C., & Sobell, M. B. (1992). Timeline follow-back: A technique for assessing self-reported alcohol consumption. In R. Z. Litten, & J. P. Allen (Eds.), *Measuring alcohol consumption; psychosocial and biochemical methods* (Vol. 17, pp. 41–72). Totowa, NJ: Humana Press.

Sobell, L. C., & Sobell, M. B. (1995). *Alcohol timeline followback users' manual Toronto*. Canada: Addiction Research Foundation.

Sobell, L. C., & Sobell, M. B. (2000). *Alcohol timeline followback recall aids*. Nova Southeastern University, Center for Psychological Studies. Available at: http://www.nova.edu/gsc/forms/timeline-followback-forms.html.

Sobell, L. C., & Sobell, M. B. (2004). Alcohol consumption measures. In J. P. Allen, & M. Columbus (Eds.), *Assessing alcohol problems: A guide for clinicians and researchers* (pp. 55–74). Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism.

Viljoen, D. L., Gossage, J. P., Brooke, L., Adnams, C. M., Jones, K. L., Robinson, L. K., et al. (2005). Fetal alcohol syndrome epidemiology in a South African community: A second study of a very high prevalence area. *Journal of Studies on Alcohol, 66*, 593–604.

de Visser, R. O. (2015). Personalized feedback based on a drink-pouring exercise may improve knowledge of, and adherence to, government guidelines for alcohol consumption. *Alcoholism: Clinical and Experimental Research, 39*, 317–323. http://dx.doi.org/10.1111/acer.12623.

Zelner, I., Kenna, K., Brien, J. F., Bocking, A., Harding, R., Walker, D., et al. (2013). Meconium fatty acid ethyl esters as biomarkers of late gestational ethanol exposure and indicator of ethanol-induced multi-organ injury in fetal sheep. *PLoS One, 8*, e59168. http://dx.doi.org/10.1371/journal.pone.0059168.

Paediatric and Perinatal Epidemiology
Affiliated to the Society for Pediatric and Perinatal Epidemiologic Research

doi: 10.1111/ppe.12136

Study Design Article

The Safe Passage Study: Design, Methods, Recruitment, and Follow-Up Approach

Kimberly A. Dukes,[a] Larry Burd,[b] Amy J. Elliott,[c] William P. Fifer,[d,e] Rebecca D. Folkerth,[f,g,h] Gary D.V. Hankins,[i] Dale Hereld,[j] Howard J. Hoffman,[k] Michael M. Myers,[d,e] Hein J. Odendaal,[l] Caroline Signore,[m] Lisa M. Sullivan,[n] Marian Willinger,[m] Colleen Wright[o,p], Hannah C. Kinney[g,h]
for the PASS Research Network

[a]*DM-STAT, Inc., Malden*
[f]*Department of Pathology, Brigham and Women's Hospital*
[g]*Department of Pathology, Boston Children's Hospital*
[h]*Harvard Medical School*
[n]*Department of Biostatistics, Boston University School of Public Health, Boston, MA*
[b]*University of North Dakota Medical School, Grand Forks, ND*
[c]*Center for Health Outcomes and Prevention, Sanford Research, Sioux Falls, SD*
[d]*Departments of Psychiatry and Pediatrics, Columbia University*
[e]*New York State Psychiatric Institute, New York, NY*
[i]*Medical Branch, University of Texas, Galveston, TX*
[j]*National Institute on Alcohol Abuse and Alcoholism, Rockville*
[k]*Epidemiology and Statistics Program, Division of Scientific Programs, National Institute on Deafness and Other Communication Disorders*
[m]*Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD*
[l]*Department of Obstetrics and Gynecology*
[o]*Department of Pathology, Faculty of Medicine and Health Science, Stellenbosch University, Stellenbosch, Western Cape*
[p]*National Health Laboratory Services, Port Elizabeth, Eastern Cape, South Africa*

Abstract

Background: The Safe Passage Study is a large, prospective, multidisciplinary study designed to (1) investigate the association between prenatal alcohol exposure, sudden infant death syndrome (SIDS), and stillbirth, and (2) determine the biological basis of the spectrum of phenotypic outcomes from exposure, as modified by environmental and genetic factors that increase the risk of stillbirth, SIDS, and in surviving children, fetal alcohol spectrum disorders.

Methods: The results provided are based on an interim assessment of 6004 women enrolled, out of the 12 000 projected, from the Northern Plains, US, and Cape Town, South Africa, areas known to be of high risk for maternal drinking during pregnancy. Research objectives, study design, and descriptive statistics, including consent, recruitment, and retention information, are provided.

Results: Overall visit compliance is 87%, and includes prenatal, delivery/newborn, and postnatal contacts through 1 year post-delivery. Pregnancy outcome ascertainment is 98% prior to medical chart review; less than 2% of women withdraw. Consent for the use of DNA and placental tissue exceed 94%, and consent to participate in the autopsy portion of the study is 71%.

Conclusions: The Safe Passage Study is the first multi-site study of SIDS and stillbirth to integrate prospectively collected exposure information with multidisciplinary biological information in the same maternal and fetal/infant dyad using a common protocol. Essential components of the study design and its success are close ties to the community and rigorous systems and processes to ensure compliance with the study protocol and procedures.

Correspondence:
Kimberly A. Dukes, DM-STAT, Inc., One Salem Street, Suite 300, Malden, MA 02148-5229, USA.
E-mail: kim.dukes@dmstat.com

Keywords: *PASS, Safe Passage Study, fetal alcohol spectrum disorders, prenatal alcohol exposure, stillbirth, sudden infant death syndrome, study methodology.*

Prenatal alcohol exposure (PAE) is a major public health concern in the US; 52% of women report drinking alcohol during their childbearing years and 8% report drinking during pregnancy.[1] Fetal alcohol spectrum disorders (FASD) is the umbrella term that encompasses a continuum of neurodevelopmental disabilities, craniofacial and somatic anomalies, and growth impairments attributed to the toxic effects of PAE, affecting 1% of individuals in the US.[2] Diagnoses that fall under FASD include fetal alcohol syndrome (FAS), partial FAS, alcohol-related neurodevelopmental disorder, and alcohol-related birth defects.[3] Emerging reports suggest an association between PAE and stillbirth and sudden infant death syndrome (SIDS), indicating that fetal and infant *mortality*, as well as neurodevelopmental *morbidity*, may be part of the spectrum of adverse outcomes.[4,5]

The global burden of stillbirth is large, with approximately 2.65 million third trimester stillbirths annually.[6] In the US, stillbirth is defined as fetal death at or beyond 20 weeks gestation. SIDS is defined as the sudden death of an infant under 1 year of age that remains unexplained after a thorough case investigation, including the performance of a complete autopsy, an examination of the death scene, and a review of the infant's clinical history.[7] SIDS is the leading cause of postneonatal mortality in the US (overall infant mortality rate: 53.9 per 100 000 livebirths; postneonatal mortality rate: 49.1 per 100 000 livebirths).[8]

Virtually all existing evidence of PAE's effect on early mortality is based on retrospective studies, and is often compromised by insufficient power and recall bias related to quantity, frequency, and timing of exposure.[4,5,9] Recognising the need to elucidate the role of PAE in early mortality, as well as neurodevelopmental morbidity in survivors, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) established a cooperative agreement in 2003 for the Prenatal Alcohol in SIDS and Stillbirth (PASS) Network. The National Institute on Deafness and Other Communication Disorders (NIDCD) joined the PASS Network in 2011. The objectives of the prospective Safe Passage Study conducted by the PASS Network are to (1) investigate the association between PAE, SIDS, and stillbirth, and (2) determine the biological basis of the spectrum of phenotypic outcomes from exposure, as modified by environmental and genetic factors that increase the risk of stillbirth, SIDS, and in surviving children, FASD. Women at high risk for maternal drinking during pregnancy are recruited in the Northern Plains (NP), US, and in Cape Town, South Africa (SA).[9,10] The results provided are based on an interim assessment of 6004 women (half of the target) enrolled, and include an overview of the research objectives, study design, and descriptive statistics, including consent, recruitment, and retention information.

Methods

Overview of the PASS Network

The PASS Network is a collaborative effort among the NICHD, NIAAA, and NIDCD; two comprehensive clinical sites (CCS), one in the NP, US, and the other in Cape Town, SA; a developmental biology and pathology centre; a physiology assessment centre; and a centralised data coordinating and analysis centre. Internal network oversight is provided by the steering committee, and external oversight is provided by an independent advisory and safety monitoring board, as well as numerous institutional review boards (IRBs) and tribal communities.

Hypotheses

The primary hypothesis of the Safe Passage Study is that PAE increases the risk for SIDS and stillbirth. Multiple secondary hypotheses are based upon the premise that in addition to FASD, some stillbirths and SIDS cases may be part of a spectrum of disorders that result from PAE in combination with other maternal, environmental, and genetic factors that impinge directly on the central or autonomic nervous systems of the fetus, or secondarily upon the fetus via placental mechanisms. The secondary hypotheses relate to interactions among PAE and maternal, environmental, and genetic factors as modifiers of the function and structure of the placenta, development of the fetal and infant face and brain (three-dimensional ultrasound), autonomic function in the fetus and

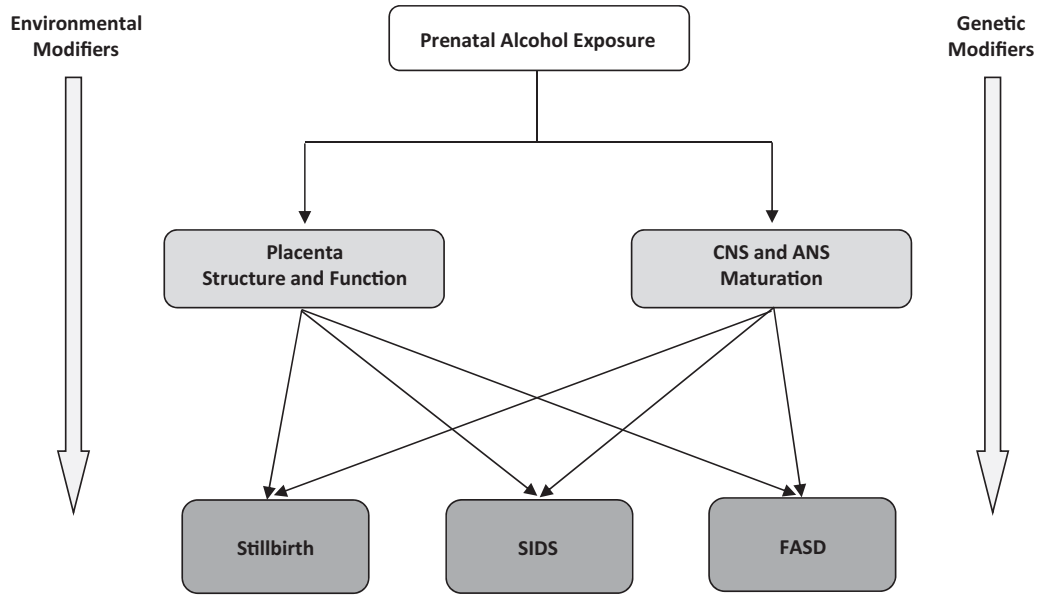

Figure 1. Model of adverse perinatal outcomes related to prenatal alcohol exposure and the role of environmental and genetic modifiers. ANS, autonomic nervous system; CNS, central nervous system.

infant, cortical and brainstem activity in the infant [electroencephalography (EEG) and auditory function pathway assessments, respectively], and neurotransmitter and synaptic maturation in the cerebral cortex and brainstem of the fetus and infant (Figure 1).

Design

The planned enrolment period for the Safe Passage Study is 7.5 years, from August 2007 to January 2015, with subsequent follow-up for 1 year post-delivery. The main study protocol is implemented for 12 000 pregnant women enrolled in the study, while an embedded study protocol includes a randomly selected subset of 3750 women who were enrolled prior to 24 weeks gestation and consented to additional study assessments. The incorporation of the embedded study provides more in-depth information pertinent to specific secondary hypotheses, while minimising costs and resources.

Power calculations utilised published rates of SIDS, stillbirth, and PAE (see Table 1 and Supporting Information Appendix S1) and information from a retrospective study of antecedent risk factors for SIDS in the NP American Indians [Aberdeen Area Infant Mortality Study (AAIMS)] reporting a relative risk (RR) of 6.7 for SIDS among women with PAE in the first trimester as compared to unexposed women.[9] Conservatively assuming that the risk of SIDS is tripled, 49% of women will be exposed to PAE during pregnancy, and 10% attrition, 11 622 women were required. The targeted sample size of 12 000 women enrolled (7000 from SA and 5000 in the NP) is expected to yield a sample of 98 stillbirths and 37 SIDS cases to ensure 80% power to detect an RR of 3 with a chi-square test for proportions with continuity correction and a

Table 1. Published sudden infant death syndrome (SIDS), stillbirth, and fetal alcohol syndrome (FAS) rates

Parameter	Overall US	American Indians in Northern Plains, US	Mixed ancestry in South Africa
Any drinking during pregnancy	8.0%[1]	57.6%[9]	40.5%[10]
SIDS rate	0.53/1000[11]	3.46/1000[9]	3.41/1000[12]
Stillbirth rate	6.2/1000[13]	8/1000[14]	15/1000[15]
FAS rate	0.5–2.0/1000[16]	3.9–8.5/1000[17,18]	40.5–46.4/1000[10]

two-sided level of significance of 5%. Based on the rates of stillbirth reported in Table 1 (8/1000 and 15/1000 in the NP and SA, respectively),[14,15] a sample size of 12 000 will ensure >95% power to detect an RR of at least 2 comparing women with PAE with those without PAE. The study is not designed to investigate genetic and biological interactions or perform subgroup analyses (e.g. by site, cause of death). However, these relationships will be explored as appropriate.

Recruiting, screening, and enrolment

Each CCS is responsible for recruiting, enrolling, and following participants in accordance with the common study protocol and for disseminating information back to participating communities. The *Northern Plains CCS* is comprised of five clinical sites in North Dakota and South Dakota, including two sites on American Indian Reservations. The *Stellenbosch CCS* recruits from Bishop Lavis and Belhar residential areas within Cape Town, SA, and serves mainly the mixed ancestry population.[19]

Screening and enrolment occur at prenatal clinics affiliated with each CCS between 6 weeks gestation up to, but not including, delivery. During the recruitment or enrolment visit, participants provide informed consent that includes consent for specific study components/assessments (e.g. collection of placental tissue, use of specimens for future studies, contact for future studies) and authorisation for the collection of personally identifiable information. Women are provided these options so that they can decline aspects of the study that conflict with their personal needs or cultural beliefs. In the event of fetal or infant demise, a separate informed consent is required for collection of autopsy tissue, and access to the autopsy report and death scene investigation (infant demise only) for research. Of the participants who enrol prior to 24 weeks gestation, one in three are randomly selected and invited to participate in the embedded study. Educational materials on the potential effects of alcohol and tobacco exposure during pregnancy and safe sleeping practices for infants are provided to all participants.

Inclusion and exclusion criteria

A woman is eligible if all of the following criteria are met: (1) able to provide informed consent, (2) pregnant with one or two fetuses, (3) 16 years of age or older, (4) gestational age of at least 6 weeks, 0 days and not at the delivery admission, and (5) able to speak English or Afrikaans. A woman is excluded if any of the following criteria are met: (1) planned abortion, (2) planned relocation from catchment area prior to delivery, or (3) advice against participation by a health care provider (e.g. requires additional medical care).

Schedule of evaluations and events

Overview

The Safe Passage Study common protocol was developed and is maintained by the PASS Network steering committee. There are three clinical assessment periods: prenatal, delivery/newborn, and postnatal (Figure 2). Depending on the timing of enrolment, women have up to three prenatal visits: 20–24 weeks, 28–32 weeks (embedded study only), and 34+ weeks. Clinical coordinators at each CCS monitor labour and delivery admissions daily to determine if a study participant has delivered, and if so obtain pregnancy outcome information. If a liveborn infant is delivered preterm (prior to 37 weeks gestation), the newborn visit and all subsequent postnatal visits are adjusted for prematurity (39–41 weeks gestational age-adjusted interval). Postnatal visits occur at 1 month and 1 year, and at the 1 year visit, confirmation as to whether the infant is alive is made through personal contact and by review of both death records and medical charts. PASS personnel receive notifications of infant demises through well-established relationships with the forensic officers in the catchment areas.[20] Upon notification of demise, an attempt is made to immediately consent women for the fetal or infant demise arm of the study. At any time during the study, the participant may withdraw.

Assessments (Figure 2)

Self-reported maternal characteristics (e.g. demographics, medical, and obstetric history), and dietary and psychosocial (i.e. depression, resilience, traumatic and threatening experiences, anxiety, and perceived stress) information, are collected at the earliest prenatal visit. Anthropometry, self-reported exposure (e.g. alcohol, tobacco, marijuana, methamphetamines), and fetal physiology [e.g. heart rate (HR), heart rate variability (HRV), movement, HR-movement coupling]

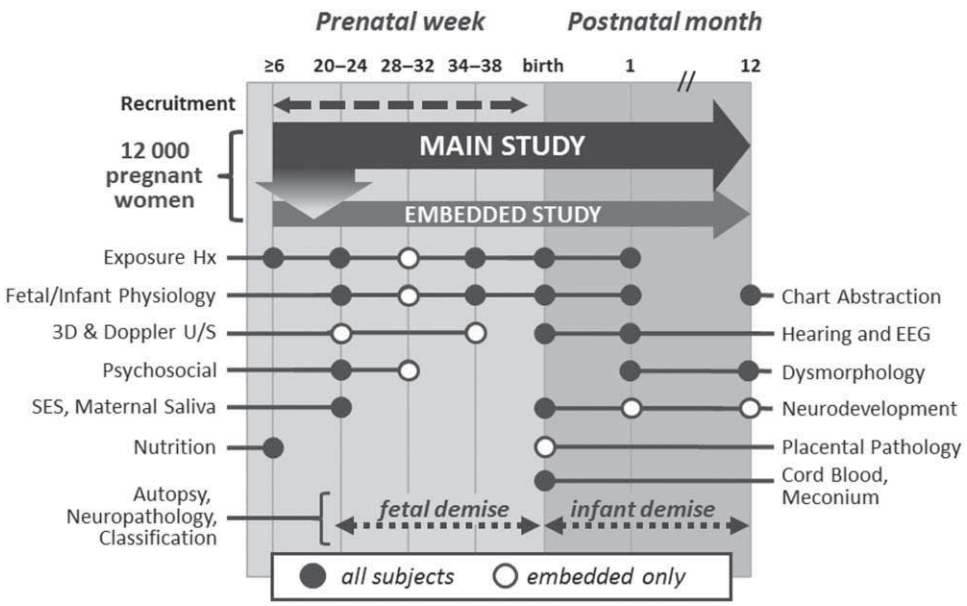

Figure 2. Schedule of evaluations and events. Hx, history; U/S, ultrasound.

are collected at each prenatal visit. Biometry and Doppler ultrasound velocimetry of uterine and fetal vessels are performed for embedded study participants. Postnatal newborn and/or 1 month visits include autonomic, cardiorespiratory, cortical activity, and auditory assessments, self-reported exposure, infant care practices, infant anthropometrics, facial dysmorphology photographs, and the Amiel-Tison Neurologic Assessment at term.[21] At the 1 year visit, the Mullen Scales of Early Learning[22] is administered to assess cognitive ability and motor development (embedded study), and infant anthropometrics and facial dysmorphology photographs are collected. Maternal (pregnancy through delivery) and infant (newborn to 1 year) charts are abstracted to obtain information regarding growth, physical exam/fetal structure, laboratory testing, medications and interventions, clinical events, co-morbidities, and diagnoses. Serious adverse events, unanticipated problems, and concomitant services are collected at each participant visit, contact, or event, and are reported according to regulatory guidelines.

Alcohol exposure assessment

Alcohol exposure information is captured using the validated Timeline Follow-Back (TLFB) method.[23,24] At each prenatal visit, this information is collected for the last reported drinking day (and 30 days prior). Additionally, at the recruitment interview, peri-conception (2 weeks prior and 2 weeks following the last menstrual period) alcohol intake is collected. Detailed information is obtained to standardise and calculate the total grams of alcohol consumed on each drinking day or episode.[25] Specifically, the type(s) of alcoholic beverage consumed, whether the drink was frozen or included ice, number and size of containers, number of persons sharing, and duration is collected for each drinking day. Total grams of alcohol consumed per drink is calculated and converted into standard drinks using the NIAAA definition of one standard drink equals 14 g of pure alcohol.[25]

Physiology assessments

The *Physiology Assessment Center* (PAC) leads the investigation into the relationship between potential adverse effects of PAE (alone or in combination with other exposures) and autonomic, respiratory, and brain function in the fetus and infant, as these effects may impair central homeostatic regulation and increase the risk for stillbirth and SIDS. Measures of fetal HR, HRV, movement, and HR-movement coupling are assessed at up to three fetal visits using ultrasound. Beat-to-beat variability in the fetus and mother are collected simultaneously using a transabdominal fetal electrocardiograph. Infant measures of cardiorespiratory function during sleep, as well as responses to head-up tilt challenge, are obtained at the newborn and 1 month visits. During the infant visits, cortical

activity (EEG) and auditory function [auditory brainstem responses (ABR) and transient evoked otoacoustic emissions (TEOAE)] are assessed.

Developmental biology and pathology assessments

The *Developmental Biology and Pathology Center* (DBPC) leads the investigation into the potential adverse effects of PAE (alone or in combination with other exposures) upon the placenta and developing fetal and infant brain. The main objectives of the neuropathological studies are to determine the relationship between PAE and the (1) neurotransmitter development of brainstem sites that control homeostatic function, relative to SIDS and stillbirth, and (2) neurotransmitter development and synaptogenesis in areas of the cerebral cortex related to abnormal cognitive function in individuals with FASD. Genetic research includes investigating the effect of PAE and modifications to genetic mechanisms that impact phenotypic outcomes (i.e. stillbirth, SIDS, or FASD). For each demise, all relevant clinical, autopsy, and other pertinent (death scene investigation, placental pathology) information is reviewed by the pathology subcommittee led by the DBPC, and comprised of experts in paediatrics, obstetrics, dysmorphology, genetics, paediatric/placental pathology, paediatric neuropathology, and forensic pathology. The demises are classified according to previously published systems, as well as a stillbirth classification system developed for the study (see Supporting Information Appendix S1).[7,26–30] Demise adjudication requires 100% consensus while blinded to prenatal exposures. Specimens collected for the Safe Passage Study include maternal and infant saliva or umbilical cord blood for DNA analysis (all participants), meconium (all), placental samples (embedded study), and brain samples (autopsied stillbirths and infant demises). Specimens are shipped for long-term storage to Fisher Bioservices in Rockville, MD.

Biostatistics, regulatory compliance, quality assurance, and data management

The *Data Coordinating and Analysis Center* (DCAC) is responsible for the study design and data analysis, biostatistical issues, and the development of systems and processes to provide centralised data management and ensure compliance with good clinical practices[31] and regulatory guidelines. The DCAC oversees (1) the development and maintenance of the common protocol, ancillary studies, consent forms, manual of operations, and regulatory binder, and ensures that yearly IRB protocol and consent form approvals are completed and documented at each site/centre; (2) the development and maintenance of all case report forms (CRFs) and electronic web-based tracking, data entry, and reporting systems; and (3) quality assurance monitoring of all protocols and study procedures, as well as monitoring of statistical assumptions utilised to size the study.

Statistical methods

The results presented are based on an interim (halfway through enrolment target, $n = 6004$) assessment and are descriptive in nature, and as agreed by the steering committee do not include information regarding exposure or outcome rates related to the primary hypothesis. Reporting results on exposure or primary outcome information prior to study completion may bias or impact recruitment and retention of participants, cause therapeutic drift (i.e. alter medical provider practices at a given site/centre), alter the focus of information collected by study staff, or alter participant report. Analyses were performed using SAS/STAT® software, Version 9.3, Copyright © 2011 (Cary, NC, US).

Results

Screening, consent, and enrolment

As of 7 July 2011, 9753 women were approached and 6004 were enrolled (Figure 3); these women and their infants were followed for one age-adjusted year post-delivery (through 5 April 2013). The enrolled women represent three diverse populations: Caucasians (25%), American Indians (17%), and women of mixed ancestry (57%) [other/not specified (1%)]. Of the 26% of women who refused to participate, most indicated a lack of interest (65%) or time (25%).

Of the 6004 women enrolled in the study, 99% agreed to participate in all study components/evaluations (Figure 2), with the exception of collection of placental tissue (94% agreed), use of specimens for future studies (96% agreed), and contact for future studies (96% agreed). Consent rates to be contacted for future studies were mixed ancestry (98%), Caucasian

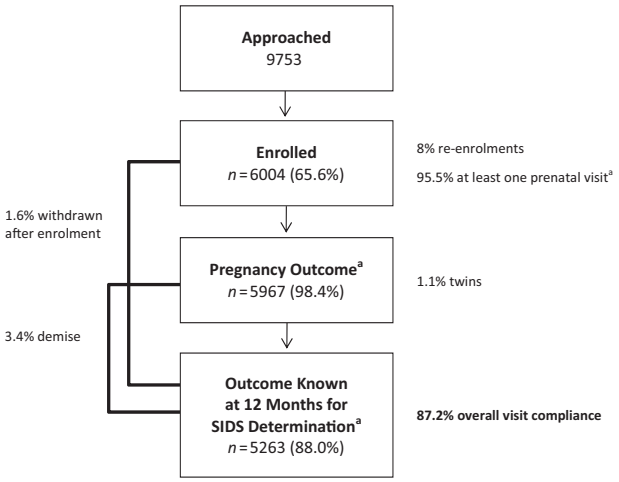

Figure 3. Consolidated standards of reporting trials chart. [a]Of those eligible for the contact.

(92%), and American Indian (94%). Consent rates for collection of placental tissue were mixed ancestry (90%), Caucasian (100%), and American Indian (96%). Of the parents who experienced a fetal or infant demise, 71% consented to participate in the autopsy portion of the study, and of those, 92% provided consent to brain tissue donation and 84% to specimen use in future studies.

Participant characterisation, follow-up information, and compliance rates

The 6004 women enrolled represent 6066 infants/fetuses (1.1% were twin pregnancies) and 95 (1.6%) women withdrew consent (Figure 3). Women were 25.9 ± 5.8 (mean ± standard deviation) years of age at the time of enrolment. High school completion rates were Caucasian (96%), American Indian (57%), and mixed ancestry (23%). The overall visit compliance was 87.2% for all visits, including prenatal, delivery/newborn, and postnatal contacts (Table 2). Over 95% of women completed at least one prenatal study visit in addition to the recruitment interview. Pregnancy outcome was obtained in 98% of women prior to review of medical records. Women delivered at 39.0 ± 2.1 weeks gestation; 12% delivered preterm. The newborn or 1 month assessment was completed for 96% of women, and the 1 year outcome has been ascertained on 88%; the latter has increased to over 90% in the past year (data not shown). Approximately 3% of the participants experienced a fetal or infant demise. Visit compliance for American Indian women (72%) was lower on every scheduled assessment compared with Caucasian and mixed ancestry women (89% and 91%, respectively) (Table 2). Over 48 000 fetal (21 505) and infant (27 268) physiology files, 145 911 CRFs, 2359 ultrasounds, 20 183 specimens, and 46 286 infant photographs have been collected and are currently being analysed.

Comments

The Safe Passage Study is the first multi-site study of SIDS and stillbirth to integrate prospectively collected adverse exposure information with multidisciplinary biological information in the same maternal and fetal/infant dyad using a common protocol. The collection of physiological assessments of fetuses and infants who may succumb to stillbirth or SIDS is unique, may identify abnormal physiological profiles of risk for early death, and will produce the largest database of prospective serial HR, HRV, respiratory patterns, tilt responses, EEGs, ABRs, and TEOAEs available to date. These rich physiological data, linked with prospectively collected serial exposure information, will provide critically needed information about the effect of PAE upon a spectrum of neural processes. The neuropathological studies are also unique in that they represent the first ever analysis of prospectively collected exposure information linked with cellular, neurochemical, and molecular parameters in the *human* brain in autopsied fetuses and infants. The linkage of neuropathological studies with prospectively collected physiological information has the potential to increase our understanding of the pathological mechanism of SIDS, which has remained elusive for decades. A potential significant contribution of the Safe Passage Study is the development of algorithms for the early identification of fetuses and infants potentially at risk for adverse outcomes, such as stillbirth, SIDS, and FASD. The risk profile will be based upon the analysis and integration of physiological profiles in the fetus/infant and placental, genetic, and maternal factors. The PASS Network will comply with the data sharing policy of the National Institutes of Health (NIH). Availability of tribal data will be dependent upon the requirements of the tribal review boards.

The reliability and validity of maternal self-reported exposure and biomarkers to detect exposure during pregnancy vary among study designs.

Table 2. Visit compliance by race

		American Indian $n = 1042$	Mixed ancestry $n = 3410$	Caucasian $n = 1493$	Other $n = 47$	Total $n = 5992$
Overall participant compliance	Mean (SD) median	69.1 (29.3) 80.0	90.7 (17.1) 100.0	87.6 (21.0) 100.0	74.8 (29.7) 84.5	86.1 (22.2) 100.0
Overall visit compliance	# compliant/# eligible	4248/5909	17 799/19 552	8125/9087	209/275	30 381/34 823
	(%)	(71.9%)	(91.0%)	(89.4%)	(76.0%)	(87.2%)
20–24 weeks	# compliant/# eligible	644/848	2031/2173	1303/1442	33/38	4011/4501
	(%)	(75.9%)	(93.5%)	(90.4%)	(86.8%)	(89.1%)
28–32 weeks[a]	# compliant/# eligible	307/380	924/951	540/578	13/17	1784/1926
	(%)	(80.8%)	(97.2%)	(93.4%)	(76.5%)	(92.6%)
34+ weeks	# compliant/# eligible	714/893	3023/3151	1267/1352	39/44	5043/5440
	(%)	(80.0%)	(95.9%)	(93.7%)	(88.6%)	(92.7%)
Delivery	# compliant/# eligible	809/967	3180/3340	1387/1442	35/45	5411/5794
	(%)	(83.7%)	(95.2%)	(96.2%)	(77.8%)	(93.4%)
Newborn	# compliant/# eligible	686/931	2667/3324	1288/1412	28/43	4669/5710
	(%)	(73.7%)	(80.2%)	(91.2%)	(65.1%)	(81.8%)
1 month	# compliant/# eligible	527/949	3003/3320	1202/1433	34/44	4766/5746
	(%)	(55.5%)	(90.5%)	(83.9%)	(77.3%)	(82.9%)
12 months	# compliant/# eligible	561/941	2971/3293	1138/1428	27/44	4697/5706
	(%)	(59.6%)	(90.2%)	(79.7%)	(61.4%)	(82.3%)
Participants with at least one prenatal visit	# compliant/# eligible	868/998	3232/3317	1431/1478	43/46	5574/5839
	(%)	(87.0%)	(97.4%)	(96.8%)	(93.5%)	(95.5%)
Participants with pregnancy outcome ascertained[b]	# compliant/# eligible	995/1042	3403/3410	1450/1493	47/47	5895/5992
	(%)	(95.5%)	(99.8%)	(97.1%)	(100.0%)	(98.4%)
Outcome known at 12 months for SIDS determination	# compliant/# eligible	937/1037	2965/3408	1324/1492	37/47	5263/5984
	(%)	(90.4%)	(87.0%)	(88.7%)	(78.7%)	(88.0%)
Outcome known at approximately 12 months	# compliant/# eligible	937/1037	3156/3408	1324/1492	38/47	5455/5984
	(%)	(90.4%)	(92.6%)	(88.7%)	(80.9%)	(91.2%)

The number displayed in each column header represents the total number of women enrolled with a recruitment visit. The compliance computations account for whether the participant was due for the study visit.

[a]Applies to the *embedded study* only.

[b]In the case of twins, a participant will have two deliveries. Of the outcomes ascertained, there were 5956 total deliveries.

As compared with biomarkers, the granular detail with respect to timing, frequency, and amount of exposure is more easily obtained through self-report.[32] However, there are inherent issues with self-report, such as recall bias,[33] fear of social stigma, punishment, guilt, and other factors.[32,34] Further, data collected during pregnancy as compared with post pregnancy have demonstrated issues with test–retest reliability.[35] In the Safe Passage Study, women are eligible to enrol as early as 6 weeks gestation; however, it has been shown that women who are heavily exposed may not participate, may enrol later in pregnancy, or may be less compliant with visits.[36] Despite these potential limitations, the TLFB method has been widely accepted as a measure of self-reported exposure. Our data indicate that women are drinking various and sometimes hazardous amounts throughout pregnancy, and preliminary analyses demonstrate excellent performance characteristics between self-report and meconium biomarkers (PASS data, publications pending).

Over the course of the Safe Passage Study, the enrolment, follow-up, and retention rates, as well as exposure and outcome rates, have been extensively monitored and are consistent with the estimates used to size/power the study (Table 1). Given that obtaining consent for research [in particular, the use of autopsy (brain) and DNA samples] can be problematic in socio-economically disadvantaged and minority populations,[37,38] the rates in the Safe Passage Study are exceptional and attest to early involvement and ongoing commitment of the communities to the mission of the Safe Passage Study (Supporting Information Appendix S1). Based upon the experience of the clinical sites in the Safe Passage Study in obtaining autopsy tissues for research, we have reported suggested guidelines for obtaining such consent in socio-economically disadvantaged populations that we consider of potential value to investigators involved in similar types of research (Odendaal *et al*. 2011).[38]

Stillbirth, SIDS, and FASD disproportionately afflict socio-economically disadvantaged populations and minority populations.[9,10,12,14–18] However, it is likely that these findings will be universally applicable due to potential associations found between common cellular and molecular mechanisms of PAE upon the developing fetus and placenta. These findings may translate to preventive and intervention strategies in communities most burdened by these disorders and to the population at large.

Acknowledgements

The authors gratefully acknowledge the cooperation of the study participants, PASS investigators, and members of the NICHD advisory safety monitoring board: Elizabeth Thom, PhD (Chair); Reverend Phillip Cato, PhD; James W. Collins, Jr, MD, MPH; Terry Dwyer, MD, MPH; George Macones, MD; Philip A. May, PhD; Jeff Murray, MD; Richard M. Pauli, MD, PhD; Raymond W. Redline, MD; and Michael Varner, MD. The PASS Research Network is supported by the National Institute on Alcohol Abuse and Alcoholism, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and National Institute on Deafness and Other Communication Disorders through the Cooperative Agreement Mechanism (U01 HD055154, U01 HD045935, U01 HD055155, U01 HD045991, and U01 AA016501). The following institutions and researchers comprise the PASS Network (additional network members other than authors listed):

DCAC: *Biostatistics:* Tara Tripp, MA, Fay Robinson, MPH; *Project Management/Regulatory Affairs:* Julie M. Petersen, BA, Rebecca A. Young, MPH; *Data Management/Information Technology:* Travis Baker, BS, Derek Petersen, BS, Gregory Toland, MS

DBPC: *Assistant Director:* Robin L. Haynes, PhD; *Co-investigators:* David S. Paterson, PhD, Kevin G. Broadbelt, PhD, Kyriacos Markianos, PhD, Ingrid A. Holm, MD, Theonia Boyd, MD, Drucilla Roberts, MD, Richard G. Goldstein, MD, Hanno Stein, PhD; *Technicians:* Claire Maggiotto, BS, Catherine Hassett, BS

CCS NP: *Co-investigators:* Jyoti Angal, MPH, Donald Habbe, MD, H. Eugene Hoyme, MD, William Massello III, MD, Bradley Randall, MD, Mary Ann Sens, MD, PhD, Catherine Stoos, MD, Peter Van Eerden, MD; *Project Management:* Whitney Adler, BA, Elizabeth Berg, RN, Jessica Gromer, RN, Bethany Norton, MA, Liz Swenson, RN, Deb Tobacco, MA

CCS SA: *Co-investigator and Project Manager:* Coen Groenewald, MBChB, MMed, FCOG environmental, M Comm; *Project Management:* Erna Carstens, RN, Jean Coldray, Nat Dipl, Mandy Potter, RN, Lucy Brink, MSc, Rosemary Meyer, BTech, Carlie du Plessis, RN, Elaine Geldenhuys, Nat Dipl

PAC: *Project Management:* J. David Nugent, BA, Carmen Condon, BA; *Data Analysis:* Margaret C. Shair, BA, Tracy Thai, BA

NIH: *Project Scientist:* Chuan-Ming Li, MD, PhD (NIDCD); *Program Officers:* Bill Dunty, PhD (NIAAA), Tonse Raju, MD, DCH (NICHD), Gordon B. Hughes, MD (NIDCD)

Further, the following individuals made significant contributions to the research and warrant recognition:
DCAC: Idania Ramirez, MPH, Jamie Collins, MA, Laura Spurchise, MPH
DBPC: Richard A. Belliveau, BA, Kristin McMillan, BA, Megan Minter, MS
PAC: Johnston T. Grier, BA, Emilia F. Vignola, BA, Joseph J. Violaris, BA

The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the Indian Health Service (IHS) or the National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Development (NICHD), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), or the National Institute on Deafness and Other Communication Disorders (NIDCD).

References

1 Centers for Disease Control and Prevention. Alcohol use and binge drinking among women of childbearing age – United States, 2006–2010. *MMWR. Morbidity and Mortality Weekly Report* 2012; 61:534–538.
2 Warren KR, Hewitt BG. Fetal alcohol spectrum disorders: when science, medicine, public policy, and laws collide. *Developmental Disabilities Research Reviews* 2009; 15:170–175.
3 Hoyme HE, May PA, Kalberg WO, *et al*. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 Institute of Medicine criteria. *Pediatrics* 2005; 115:39–47.
4 Kesmodel U, Wisborg K, Olsen SF, Henriksen TB, Secher NJ. Moderate alcohol intake during pregnancy and the risk of stillbirth and death in the first year of life. *American Journal of Epidemiology* 2002; 155:305–312.
5 Strandberg-Larsen K, Gronboek M, Andersen AM, Andersen PK, Olsen J. Alcohol drinking pattern during pregnancy and risk of infant mortality. *Epidemiology (Cambridge, Mass.)* 2009; 20:884–891.
6 Bhutta ZA, Yakoob MY, Lawn JE, *et al*. Stillbirths: what difference can we make and at what cost? *Lancet* 2011; 377:1523–1538.
7 Willinger M, James LS, Catz C. Defining the sudden infant death syndrome (SIDS): deliberations of an expert panel convened by the National Institute of Child Health and Human Development. *Pediatric Pathology/affiliated with the International Paediatric Pathology Association* 1991; 11:677–684.
8 Heron M. Deaths: leading causes for 2009. *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System* 2012; 61:1–96.
9 Iyasu S, Randall LL, Welty TK, *et al*. Risk factors for sudden infant death syndrome among northern plains Indians. *JAMA* 2002; 288:2717–2723.
10 May PA, Brooke L, Gossage JP, *et al*. Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. *American Journal of Public Health* 2000; 90:1905–1912.
11 Mathews TJ, MacDorman MF. Infant mortality statistics from the 2006 period linked birth/infant death data set. *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System* 2010; 58:1–32.
12 Molteno CD, Kibel MA. Postneonatal mortality in the Matroosberg Divisional Council area of the Cape Western Health Region. *South African Medical Journal* 1989; 75:575–578.
13 MacDorman MF, Kirmeyer S. Fetal and perinatal mortality, United States, 2005. *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System* 2009; 57:1–19.
14 North Dakota Department of Health, Division of Vital Records. Fetal deaths by race (2000–2004) 2005.
15 Talip Q, Theron G, Steyn W, Hall D. Total perinatally related losses at Tygerberg Hospital – a comparison between 1986, 1993 and 2006. *South African Medical Journal* 2010; 100:250–253.
16 May PA, Gossage JP. Estimating the prevalence of fetal alcohol syndrome. A summary. *Alcohol Research & Health* 2001; 25:159–167.
17 Duimstra C, Johnson D, Kutsch C, *et al*. A fetal alcohol syndrome surveillance pilot project in American Indian communities in the Northern Plains. *Public Health Reports* 1993; 108:225–229.
18 Poitra BA, Marion S, Dionne M, *et al*. A school-based screening program for fetal alcohol syndrome. *Neurotoxicology and Teratology* 2003; 25:725–729.
19 City of Cape Town: Census 2011. *Trends and Change – 10 Years: Census 2001 – Census 2011*. 2012. http://www.capetown.gov.za/en/stats/Documents/2011%20Census/2011_Census_Cape_Town_Profile_Change_from_2001-2011.pdf [last accessed July 2014].
20 Dempers JJ, Folkerth RD, Kinney HC, *et al*. *The Institution of a Standardized SIDS Investigation Protocol in South Africa: Feasibility Study of 11 Cases in the Western Cape*. International SIDS Meeting, Portsmouth, England, 2008.
21 Amiel-Tison C. Update of the Amiel-Tison neurologic assessment for the term neonate or at 40 weeks corrected age. *Pediatric Neurology* 2002; 27:196–212.
22 Mullen EM. *Mullen Scales of Early Learning, Manual*, AGS edn. Circle Pines, MN: American Guidance Service, Inc., 1995.
23 Sobell LC, Maisto SA, Sobell MB, Cooper AM. Reliability of alcohol abusers' self-reports of drinking behavior. *Behaviour Research and Therapy* 1979; 17:157–160.
24 Sobell LC, Sobell MB. *Timeline Followback: A Technique for Assessing Self Reported Ethanol Consumption*, Vol. 17. Totowa, NJ: Humana Press, 1992.

25 Brick J. Standardization of alcohol calculations in research. *Alcoholism, Clinical and Experimental Research* 2006; 30:1276–1287.
26 Dudley DJ, Goldenberg R, Conway D, *et al*. A new system for determining the causes of stillbirth. *Obstetrics and Gynecology* 2010; 116 (Pt 1):254–260.
27 Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. *BMJ (Clinical Research Ed.)* 2005; 331:1113–1117.
28 Boyd T, Wright C, Colby K, *et al*. O139 PASS stillbirth classification: incorporating mechanism, etiology and recurrence. Prenatal alcohol stillbirth and SIDS (PASS) network, NIAAA/NICHD. *International Journal of Gynecology & Obstetrics* 2009; S132:133.
29 Krous HF, Beckwith JB, Byard RW, *et al*. Sudden infant death syndrome and unclassified sudden infant deaths: a definitional and diagnostic approach. *Pediatrics* 2004; 114:234–238.
30 Randall BB, Wadee SA, Sens MA, *et al*. A practical classification schema incorporating consideration of possible asphyxia in cases of sudden unexpected infant death. *Forensic Science, Medicine, and Pathology* 2009; 5:254–260.
31 *1996 International Conference on Harmonisation E-6(R1), Guidelines for Good Clinical Practice*. 1996. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf [last accessed July 2014].
32 Babor TF, Steinberg K, Anton R, Del Boca F. Talk is cheap: measuring drinking outcomes in clinical trials. *Journal of Studies on Alcohol* 2000; 61:55–63.
33 Northcote J, Livingston M. Accuracy of self-reported drinking: observational verification of 'last occasion' drink estimates of young adults. *Alcohol and Alcoholism* 2011; 46:709–713.
34 Bearer CF, Stoler JM, Cook JD, Carpenter SJ. Biomarkers of alcohol use in pregnancy. *Alcohol Research & Health* 2004; 28:38–43.
35 Jacobson SW, Chiodo LM, Sokol RJ, Jacobson JL. Validity of maternal report of prenatal alcohol, cocaine, and smoking in relation to neurobehavioral outcome. *Pediatrics* 2002; 109:815–825.
36 Cunradi CB, Moore R, Killoran M, Ames G. Survey nonresponse bias among young adults: the role of alcohol, tobacco, and drugs. *Substance Use & Misuse* 2005; 40:171–185.
37 Odendaal HJ, Elliott A, Kinney HC, *et al*. Consent for autopsy research for unexpected death in early life. *Obstetrics and Gynecology* 2011; 117:167–171.
38 Yancey AK, Ortega AN, Kumanyika SK. Effective recruitment and retention of minority research participants. *Annual Review of Public Health* 2006; 27:1–28.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Supplemental appendix.