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Associations of maternal smoking and drinking with fetal growth and placental abruption

Short running title

Maternal smoking and drinking and fetal development

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Abstract

Objective. To investigate pregnant women from the Safe Passage Study for the individual and combined effects of smoking and drinking during pregnancy on the prevalence of clinical placental abruption.

Study design. The aim of the original Safe Passage Study was to investigate the association of alcohol use during pregnancy with stillbirths and sudden infant deaths. Recruitment for this longitudinal study occurred between August 2007 and October 2016. Information on smoking and drinking was collected prospectively at up to 4 occasions during pregnancy where a modified timeline follow-back method was used to assess the exposure to alcohol. Placentas were examined histologically in a subset of pregnant women. For this study we examined the effects of smoking and drinking on fetal growth and the prevalence rate of placental abruption. High smoking constituted of 10 or more cigarettes per day and high drinking of four or more binge drinking episodes or 32 and more standard drinks during pregnancy. Placental abruption was diagnosed in two ways, by the clinical picture or the macroscopic and microscopic examination of the placenta.

Results. When compared to the non-drinking/non-smoking group, the high drinking/high smoking group were significantly older, had a higher gravidity, had a lower household income and booked later for prenatal care; fewer of them were employed and had toilet and running water facilities in their houses. Clinical placental abruption was diagnosed in 49 (0.87%) of 5,806 pregnancies. Histological examination was done in 1,319 placentas; macroscopic and microscopic diagnosis of

placental abruption was made in 8.2% and 11.9% of placentas respectively. These 49 cases were then correlated with seven smoking/drinking patterns during pregnancy. When compared to rates for no smoking/no drinking (0.11%) and low smoking/no drinking (0.55%), the prevalence rate of placental abruption was significantly higher ($p<.005$) in the low smoking/low drinking group (1.25%). There was also a significant relationship between low maternal employment and methamphetamine use with placental abruption.

Conclusion. As many conditions and habits are associated with placental abruption, it is impossible to single out one specific cause but concomitant drinking and smoking seem to increase the risk of placental abruption.

Key words: Placental abruption, cigarette smoking, alcohol, drinking,

Introduction

Although the association between cigarette smoking, placental abruption and pregnancy associated syndromes is well known,[1] more attention has recently been given to the compound effect of cigarette smoking and alcohol consumption on perinatal outcome,[2] using retrospective information. However, a recent prospective study demonstrated a compound effect of cigarette smoking and alcohol consumption on sudden infant deaths.[3]

Placental abruption and growth restriction carry the highest population-attributable risks of pregnancy disorders for stillbirths (15% and 23% respectively) in high-income countries.[4] Placental abruption complicate 0.4-1% of pregnancies and is responsible for 10% of all preterm births and 10-20% of all perinatal deaths. [5]

Placental abruption and placenta praevia are attributed causes of stillbirth in 7.5-42% of 142 studies in low- and middle-income countries included in a systematic review.[6] In Cape Town, the leading primary obstetric cause of perinatal-related losses are infections (17.3%), spontaneous preterm labor (15.1%) and antepartum hemorrhage (14.7%).[7]

Aliya et al. found that pregnant women who drank alcohol had a 33% greater likelihood of placental abruption[8] and drinking also increased the risk of placenta praevia, small-for-gestational age, preterm- and stillbirth. When compared to their non-drinking counterparts, drinkers had an OR of 1.26 (15% CI 1.22-1.31) of developing pregnancy-associated syndromes.[9]

In light of these findings we determined the combined effects of cigarette smoking and alcohol use on placental abruption and fetal growth in a community, known to have a high prevalence of continued smoking and drinking during pregnancy.[10]

Material and methods

The Safe Passage Study (SPS) of the Prenatal Alcohol in SIDS and Stillbirth Network, was a prospective, multi-center longitudinal cohort study with data collection between August 2007 and October 2016, to test the hypothesis that prenatal alcohol exposure is associated with increased risk for stillbirth and/or sudden infant death syndrome (SIDS). This sub-analysis addresses the South African SPS data where participants were recruited at a community health center in the Northern suburbs of Cape Town.

Detailed information on the socioeconomic conditions of participants was obtained at recruitment. Information on smoking and drinking was obtained at up to four occasions during pregnancy. A modified timeline follow-back method was used quantify how much alcohol pregnant women used before and during pregnancy.[11] They were also asked whether they had used recreational drugs during pregnancy or smoked the hookah, an oriental tobacco pipe with a long flexible tube which draws the smoke through water contained in a bowl.

Women who booked for antenatal care before a gestational age (GA) of 20 weeks, were randomized to the embedded study (28%) where additional assessments such as ultrasound and histological examination of the placenta were done (it would have been expensive and unnecessary to do these examinations on the whole cohort). Ultrasound examinations consisted of fetal biometry, and Doppler flow velocity waveforms of the uterine and umbilical arteries for the pulsatility index (PI) at 20-24 and 34-38 weeks. Dedicated ultrasonologists performed all the ultrasound examinations according to a strict protocol. The placenta was examined by the attending midwife for retroplacental hemorrhage, defined as dark blood clots adherent to the maternal surface, was placed in 10% buffered formalin and then sent to the pathology for a macroscopic examination by a technologist. Sections were cut from paraffin wax blocks and hematoxylin and eosin stained slides were produced for histological examination. Perinatal pathologists (CW, PS) examined the slides with no clinical history available. In all stillbirths cases the slides were also seen by external perinatal pathologists (TB, DR). Prior to and during the study quality control was ensured by checking inter-observer concordance between all pathologists with a standard of 90% for individual items.

As placental abruption requires clinical observation which is then supported by macro- and microscopic findings, we investigated both the clinical picture and

pathological findings for the diagnosis. To eliminate bias, no obstetric history was sent to the pathologist except for the ultrasound-derived GA and whether the fetus was a live or stillbirth. To fulfil the criteria for macroscopic abruption, the retroplacental hemorrhage had to cover at least 15% of the maternal surface with or without indentation of the underlying parenchyma (Figure 1a). Three microscopic criteria were assessed in addition to retroplacental bleeding, namely overlying infarction, intervillous hemorrhage or congestion, and intravillous hemorrhage (Figure 1b). Although this study preceded the currently accepted Amsterdam Placental Workshop Group Consensus Statement, these criteria are aligned to those defined in their statement.[12]. Due to a tendency to diagnose more small abruptions by histological examination, we used the clinical diagnosis for this study.[13]

All the findings were entered on a data capture sheet and essential clinical information was captured from the maternity hospital record.

Fetal growth was assessed by birthweight and z-scores of the birthweight using standards of the INTERGROWTH – 21st study.[14] As good correlation has been found between self-report of cigarette smoking and serum cotinine levels[15] and of drinking and the metabolites of alcohol in meconium,[16] we accept the reliability of self-report on which this study was based.

The association of placental abruption with smoking and drinking was assessed. according to a two-tier classification for smoking (no smoking and smoking only) and drinking (no drinking and drinking only), and according to our own seven-tier classification: 1. No drinking and no smoking (NDNS). 2. No drinking but low smoking (NDLS). 3. No drinking but high smoking (NDHS). 4. Low drinking but no smoking (LDNS). 5. High drinking but no smoking (HDNS). 6. Low drinking and smoking (LDLS). 7. High drinking and smoking (HDHS). In our classification mild smokers or drinkers or early quitters were excluded from the no exposure group, which was used as a control group. Exposure during pregnancy was assessed at over four periods: around last menstrual period (GA -15 to GA 15 for alcohol and GA –21 to GA 20 for smoking). Trimester (T) 1 (GA 0 to GA 97 days), T2 (GA 97 to GA 195 days) and T3 (GA 196 days to GA at delivery). All four periods were used to assess exposure. For example, to be classified in the non-exposed group (NDNS) women had to be unexposed during all four periods of assessment.

The smoking groups were LS (<10 daily cigarettes) and HS (10 or more daily cigarettes). The drinking groups were LD (<4 binge-drinking episodes and <32 total standard drinks (1 standard drink = 14 g absolute alcohol) during the pregnancy) and HD (≥4 binge-drinking episodes and ≥32 total standard drinks during pregnancy).

Women with twin pregnancies (50), lost-to-follow-up cases (8), withdrawals (36), miscarriages (46) and those with congenital anomalies (7) were excluded from our study (Figure 2). Only the first enrolment of multiple enrolment participants was included (981 excluded). As the use of cocaine was extremely rare in the study population, it was not examined further. Only participants from the mixed ancestry/Cape Coloured ethnic group were included as other ethnicities consisted of only 26 women (at recruitment women were asked to which ethnic group or race they belonged). Written informed consent was obtained from all participants. The study was approved by the Health Research Ethics Committee of Stellenbosch University.

Statistical analyses. All the information was entered on an Excel spread sheet. Statistical analyses were done with STATISTICA (Dell Inc. (2015). Dell Statistica (data analysis software system), version 13. software.dell.com). Descriptive analyses were done to identify outliers. Continuous variables (e.g. weight, GA) were compared among different groups with either analysis of variance (ANOVA) or with repeated measures ANOVA. Bonferroni multiple comparisons were used to identify significant differences among the means. Spearman correlations were used to measure correlation between repetitions of several response variables (e.g. birth- and placental weight). Intra-class correlations for agreement and consistency were also done.

As socioeconomic conditions and exposure to drugs varied among the seven-tier smoking and drinking groups, their associations with placental abruption were analyzed with one-way ANOVA for the continuous variables and with contingency tables for the nominal variables.

Results

After exclusions, 5,806 participants remained in the study (Figure 2). There were 49 (0.87%) cases of placental abruption according to the clinical picture and 48 cases reported after examination of the placenta by the nursing staff. Examination of 1,319 placentas by pathology revealed 108 cases of macroscopic abruption (8.2%) and 157 placentas (11.9%) of microscopic abruption.

Mean maternal age was 24.5 years, gravidity 2.1, body mass index (BMI) 25.5 kg/m^2, GA at booking 113 days, birthweight 2,982 g and GA at delivery 270.7 days.

When compared with the NDNS group, maternal age was significantly lower in NDLS, LDNS and LDLS groups and significantly higher in NDHS and HDHS groups (Fig. 3a, Table 1).
When compared with the NDNS group, gravidity was significantly lower in the LDNS group and significantly higher in the NDHS and HDHS groups (Table 1) while BMI was significantly lower in NDLS and LDLS groups (Table 1). When compared with NDNS, mean household income was significantly lower in the NDLS, LDLS and HDHS groups (Table 1, Fig. 3b). When GA at enrolment was compared, NDLS, NDHS, LDNS, LDLS and HDHS participants booked significantly later for antenatal care (Table 1).

Socioeconomic conditions as reflected by employment, running water and toilet facilities in the house differed significantly among the seven-tier groups (Table 2). The best conditions were observed in the NDNS group and the worst in the HDHS group.
The use of marijuana, methamphetamine and hookah also differed significantly between the smoking and drinking groups with the highest exposures. (Table 2).

When compared with the NDNS group, the uterine artery PI was significantly higher in the HDHS group (Table 3, Fig 4a) and that of the umbilical artery significantly higher in the LDLS and HDHS groups (Table 3, Fig 4b).

When compared with the NDNS group, the head circumference at 34-38 weeks was significantly lower in HDHS group, as were the biparietal diameters and femur length (Table 3).

When compared with the NDNS group, the percentile of the placental weight was significantly higher in the NDHS and significantly lower in the HDHS groups (Table 3), Z-scores of birth weight were significantly lower in NDLS, LDNS, HDNS, LDLS and HDHS (Table 3), and GA at delivery was significantly lower in the smoking only and both dual user groups (Table 3).

In Table 4 the two-tier smoking and drinking categories were compared. The frequency of placental abruption was significantly higher in the smokers where 13 (0.52%) of non-smokers developed an abruption, in contrast to 36 (1.15%) of smokers. Among drinkers the difference was not significant as the prevalence of abruption was 0.86% and 0.87% for non-drinkers and drinkers respectively

In the seven-tier classification, significant differences between the groups were observed (*P*=.00275). The frequency of placental abruption was 0.11% in the NDNS group in contrast to 1.25% in the LDLS group (Table 5).

Maternal age, gravidity, BMI and GA at enrolment, and availability of running water or toilet in the house and marijuana or hookah pipe use, were not associated with an increase in the frequency of placental abruption (Table 6). However, a lower maternal employment, hypertension and the use of methamphetamine were associated with an increase in the frequency of abruption.

Discussion

Differences were found in the socioeconomic conditions and recreational drug use among women with different smoking and drinking habits during pregnancy. Cigarette smoking, but not the use of alcohol, was associated with an increase in the prevalence rate of placental abruption. However, a combination of smoking and drinking seemed to increase the risk above that of smoking alone.

We found that the prevalence rate of placental abruption in this community-based study was 0.87%, which compares favorably with reported rates from other countries.[17-19] However, as we were strict in including only pregnant women with a clinical diagnosis of placental abruption, it is likely that some less severe cases were

not included in the study. For the USA and Japan the prevalence rate seems to vary around 0.9%[17,18] but a rate of 4.4% has been reported in India.[19] .[21,20] Our study confirms the reported strong association between maternal smoking and placental abruption.[21]

Except for some studies where an association between alcohol use during pregnancy and placental abruption was not found,[22] there seems to be strong support for the association when heavy drinkers are addressed.[23]

We could not demonstrate an association between maternal drinking and placental abruption. However, we found significant differences between groups in the seven-tier analysis where the large LDLS group had the highest prevalence rate of abruption. It therefore seems that the effect of smoking on the risk of placental abruption is increased when pregnant women also use alcohol during pregnancy; one wonders whether the effects of smoking were sufficiently adjusted for in retrospective studies?

Our finding that the PIs of the uterine and umbilical arteries are significantly increased in the HDHS group in contrast to the single exposure groups, demonstrates that the two exposures probably have a dual effect on early placental development, hence the association with placental abruption in smokers and drinkers.

Okah et al. were among the first researchers to report that the combined use of alcohol and nicotine on the risk of term low-birth-weight babies was more than that of either of these substances alone.[24] A subsequent review also confirmed that the combined effects on preterm delivery and fetal growth during pregnancy are more severe than the effect of drinking or smoking alone.[2] Thereafter it was also demonstrated that the effect of prenatal alcohol consumption on fetal growth restriction is potentiated by concomitant smoking.[25] More recently the same group demonstrated an association between tobacco use in pregnancy and PAS, an informal classification of disease states arising from diseased placental spiral arteries, placental ischemia, and endothelial dysfunction, in a population-based study.[9]

The strength of our study is that it was community based in a single population with a prospective collection of data in a structured format, in contrast with large epidemiological studies using retrospective collected data.

A weakness of the study is the small numbers in the high exposure groups which prevented the demonstration of a dose effect. However, it is unlikely that such a study will be done again as there is great emphasis on programs to help pregnant women to quit smoking and drinking before and during pregnancy. In addition, the study is too small to challenge the association between placental abruption and drinking.

Certain findings, such as the increase in uterine artery PI between 20 and 24 weeks' gestation in the HDHS group, and the increased prevalence rate of placental abruption in the LSLD group, in contrast to the similar effects in the smoking only and drinking only groups, seem to indicate a concomitant effect of smoking and drinking during pregnancy.

Placental abruption is a complex disease with many associations, such as the combination of smoking and drinking during pregnancy, maternal employment, hypertension, and methamphetamine use.

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Declaration of interests: None

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Brink

Lucy T. Brink with a M.Sc. in medical biochemistry (molecular genetics) and an interest in data programming and managing databases, started working as data manager for Safe Passage Study in 2005. I was responsible for data: capturing, clarifications, quality control, management, programming (excel and SAS), extraction and preparation for statistical analysis. I am currently involved in many collaborations, follow up-studies, publications and busy with my PhD: A CRITICAL ANALYSIS OF PRETERM BIRTH IN A HOMOGENEOUS COMMUNITY WITH A HIGH PREVELENCE RATE FOR PRETERM BIRTH, at SU. My promotor is Prof HJ Odendaal and my co-promotor is Prof DR Hall.

Boyd

I am the Director of the Division of Anatomic Pathology at Boston Children's Hospital and an Associate Professor of Pathology at Harvard Medical School. My research interests have been primarily clinicopathologic, and largely directed toward perinatal and placental pathology. I have particular ongoing interest in unexpected untoward outcome of phenotypically normal fetuses (intrauterine demise, neonatal morbidity, chronic neurodevelopmental delay), and the etiologies as revealed in various types of placental pathology. Within the last two years, in addition to manuscript publications, I have authored or co-authored 16 book chapters in four texts regarding placental pathology, two of which I also co-edited.

Groenewald

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CURRENT POSITION TITLE

Consultant Obstetrician and Gynecologist,
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MBChB, MMed(O&G) FCOG, MComm

1987 – 2009. Obstetrician and Gynecologist in private practice
2009 – 2017. Program Manager and Co-Investigator for the South African Comprehensive Clinical Site of the Prenatal Alcohol in Sudden Infant Death Syndrome and Stillbirth (PASS) Network. My involvement with the PASS Network has exposed me to the discipline of human subject research.
2017 - Current 2017. Consultant for Mediclinic Southern Africa on the development of an obstetric risk management project to be implemented into 44 maternity units at Mediclinic Hospitals.

Nel

Born 1943 in Zastron, South Africa. Completed M.Sc. in Mathematics 1967and D.Sc. in Mathematical Statistics at Free State University (UFS) 1972.

Lecturing Mathematics 1965-1972, senior lecturer in Statistics UFS and Stellenbosch University (US) 1973-1976, professor UFS 1977-1997, statistical researcher Clover 1998–2001, director Centre for Statistical Consultation and professor at US 2002-2008, consultant since 2009.

Visiting positions: University of Georgia during 1973, 1979; Stanford University 1984, 1995; Indiana University 1992, 1997; Scuola Matematica Interuniversitaria Perugia Italy 1999.

Fellow and honorary member SA Statistical Association, associate editor SA Statistical Journal 1982-1984, 1991-1999. Author or co-author of 76 publications.

Odendaal

Hein Odendaal is Emeritus Professor and part-time researcher in the Department of Obstetrics and Gynaecology at Stellenbosch University. Previously he was Director of the MRC Perinatal Mortality Research Unit and President of the South African College of Obstetricians and Gynaecologists. As part-time researcher, he is involved in the analyses of data from the Safe Passage Study of the PASS Network and a new study for the follow-up of children of the Safe Passage Study for Autism Spectrum Disorders. He is author or co-author of 260 peer review articles.

Roberts

Dr. Drucilla J. Roberts received her M.S. from UCLA and her M.D. from Harvard Medical School. She then did 2 years of an OB/GYN residency at the Brigham and Women's Hospital followed by an anatomic pathology residency in the same institution. After a fellowship in Women's and Perinatal Pathology, also at the Brigham and Women's Hospital she received a K award from the NICHD and completed a post-doctoral fellowship in Genetics at Harvard Medical School in the laboratory of Clifford Tabin. She has been director of Obstetric Pathology at the Massachusetts General Hospital since obstetrics was reinstated there in 1994. She has published more than 80 peer reviewed manuscripts and many chapters on perinatal pathology in well known texts. She is author and co-author of three books on placental pathology. Her interests focus on the biology of the placenta and perinatal clinic-pathologic correlations. Dr. Roberts has a longstanding commitment to global pathology and is chair of the Global Health Pathology Committee at the Massachusetts General Hospital. She has given courses in sub-Saharan Africa, mentored African pathologists, been involved in many pathology projects in sub-Saharan Africa, and is a proud member of the organization African Strategies for Advancing Pathology (ASAP).

Schubert

Pawel T. Schubert, MBChB, FCPath(SA), MMed, MScMedSc (Cytopathology), MPhil (Paed Path) is an Associate Professor in Anatomical Pathology and Head of the Cytology Unit at Tygerberg Hospital, Stellenbosch University and NHLS.
He completed his undergraduate studies at the University of Pretoria and his Anatomical Pathology specialisation at Stellenbosch University. He was appointed as consultant in 2006 and has been at Tygerberg Hospital and the NHLS ever since. He is actively involved in training registrars, particularly in cytology and paediatric/perinatal pathology.
He is actively involved with research project, with an emphasis on placental and paediatric pathology, as well as numerous cytology projects. To this end, he has numerous peer reviewed publications in the international literature.
He is also a member of the International Society of Cytology, South African Society of Clinical Cytology, and the South African Division of the International Academy of Pathology.

Wright

Professor Colleen Anne Wright

Colleen Wright is a consultant pathologist with **Lancet Laboratories, Johannesburg** as well as **Extraordinary Professor in Anatomical Pathology at the University of Stellenbosch, Cape Town and Honorary Professor in Anatomical Pathology at the University of the Witwatersrand Johannesburg.**

Her interests have over 30 years encompassed Perinatal Pathology and Cytopathology, the last decade she has dedicated the majority of her professional time to placental pathology, including research and teaching – pathologists and clinicians, the value that placental pathology brings to understanding disease processes and adverse pregnancy outcome

She has over 120 peer reviewed publications and has supervised 45 masters and doctoral dissertations.
She received the South African Medical Association Special Medical Service Award in 2010 for “her outstanding contribution to the field of Anatomical Pathology”.

Legends to figures

Figure 1 a. Placental abruption covering almost half of the surface of the placenta.

Figure 1 b. Retroplacental and intervillous hemorrhage. H and E X 40.

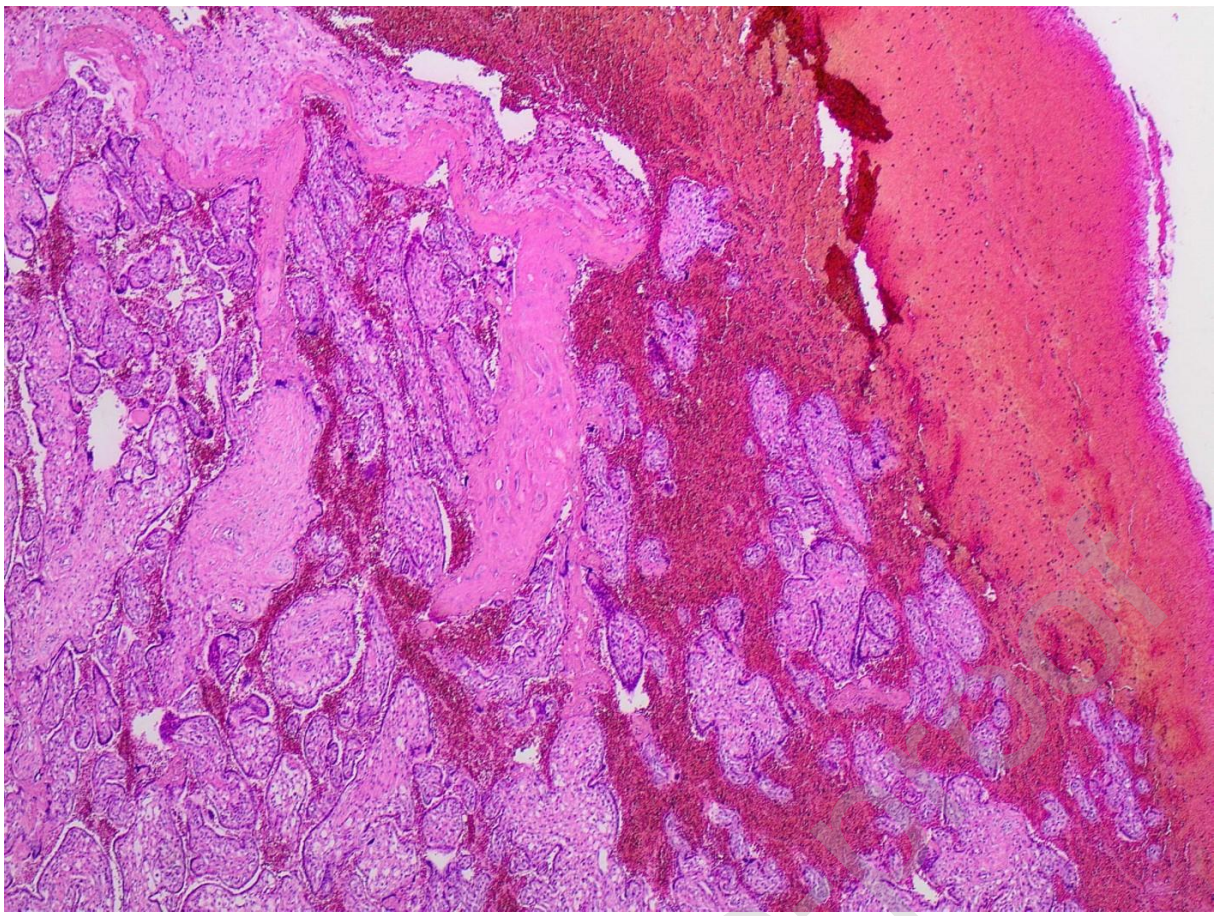

Figure 2. Study profile.

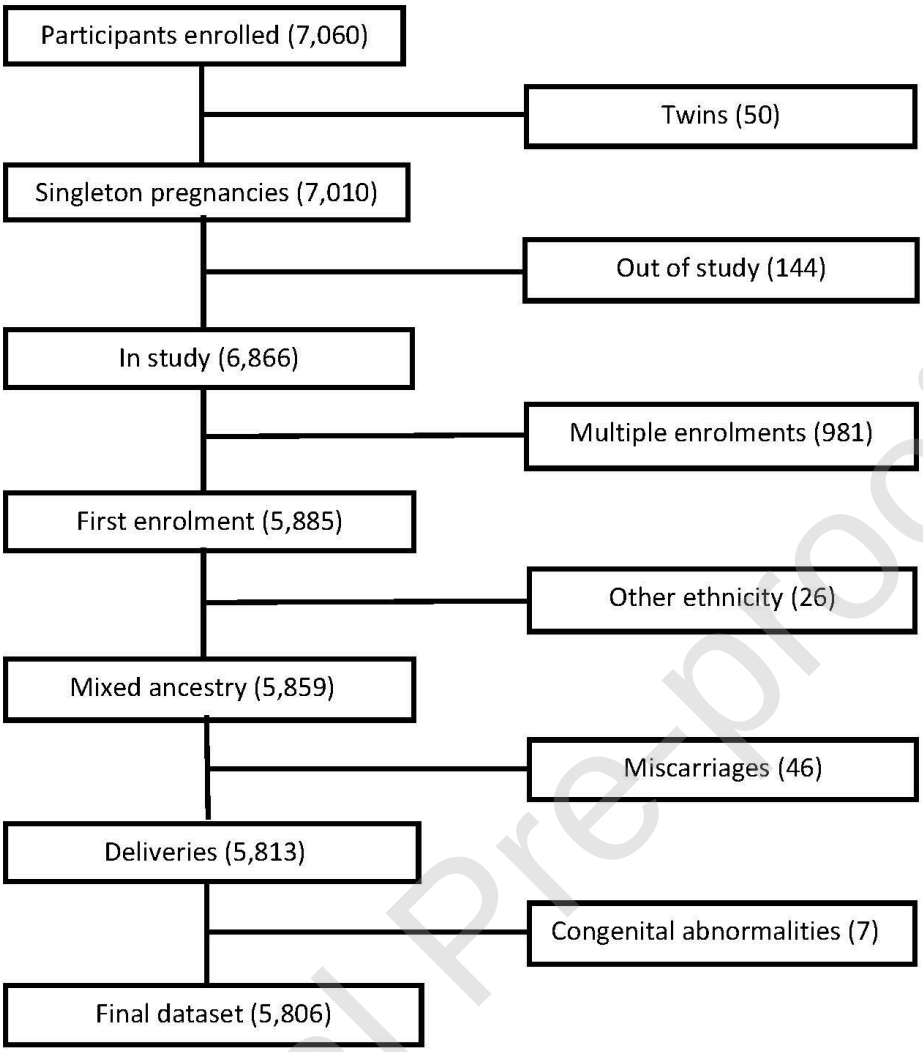

Figure 3 a. Comparison of the smoking and drinking categories regarding maternal age. Kruskal-Wallace $p<0.01$. Vertical bars denote 95% confidence intervals. Different letters above the vertical bars indicate a significant difference, while common letters indicate that these groups do not differ significantly.

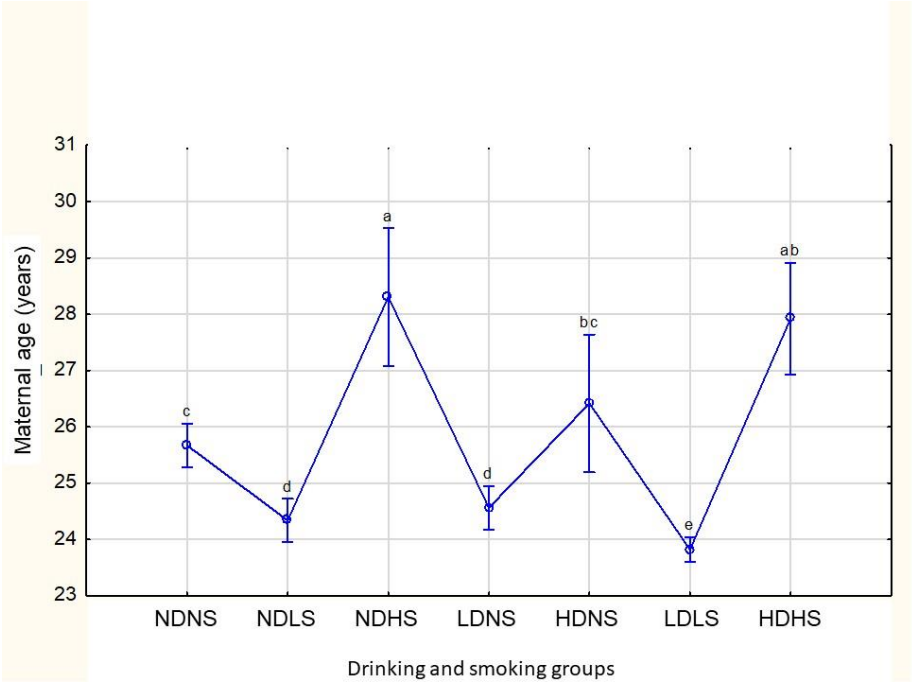

Figure 3 b. Comparison of the smoking and drinking categories regarding household income. Kruskal-Wallace p<0.01. Vertical bars denote 95% confidence intervals. Different letters above the vertical bars indicate a significant difference while common letters indicate that these groups do not differ significantly.

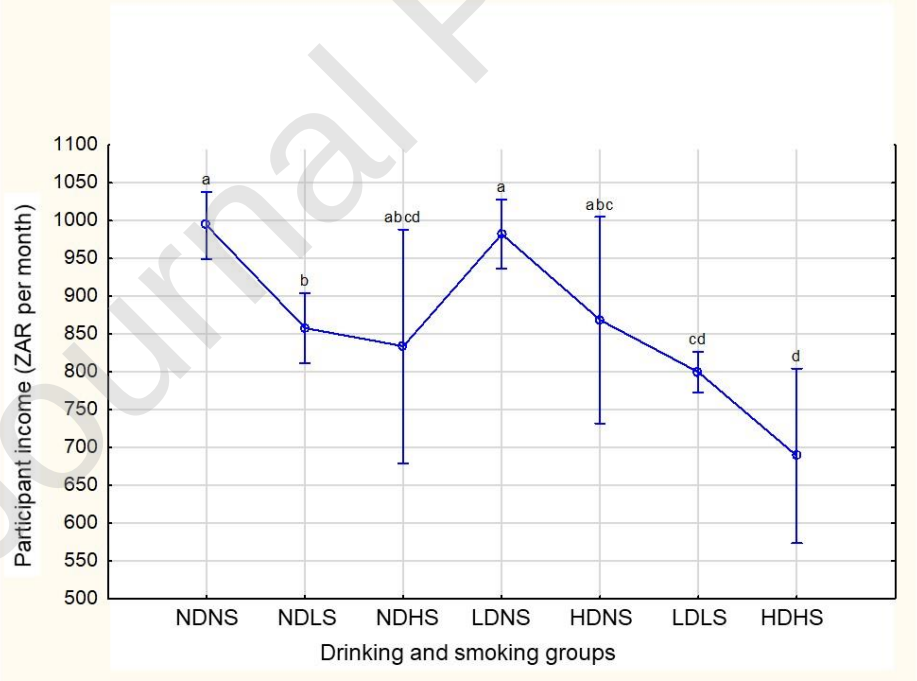

Figure 4 a. Comparison of the smoking and drinking categories regarding the pulsatility index of the uterine artery. Kruskal-Wallace p<0.05. Vertical bars denote 95% confidence intervals. Different letters above the vertical bars indicate a

significant difference while common letters indicate that these groups do not differ significantly.

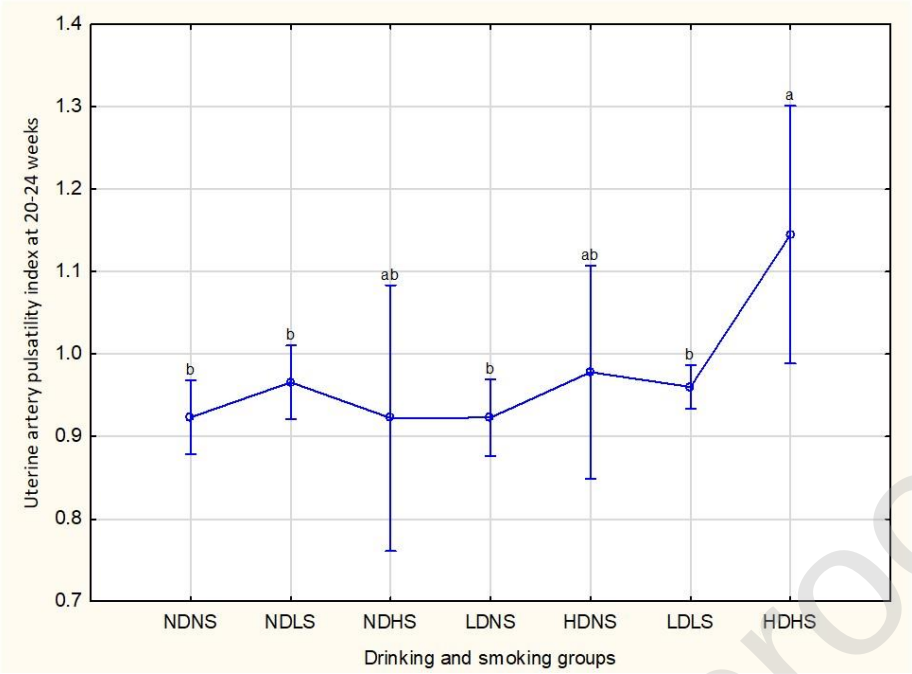

Figure 4 b. Comparison of the smoking and drinking categories regarding the pulsatility index of the umbilical artery. Kruskal-Wallace p<0.01. Vertical bars denote 95% confidence intervals. Different letters above the vertical bars indicate a significant difference while common letters indicate that these groups do not differ significantly.

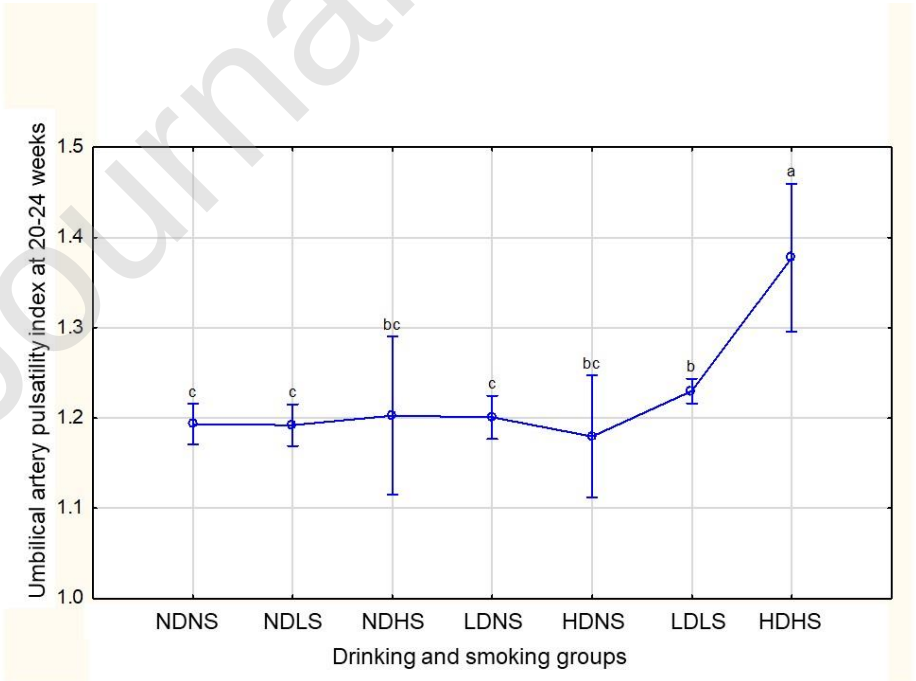

Table 1. Comparison of maternal and socioeconomic variables in the different smoking and drinking groups

Variable	F	Anova *P*	Kruskal Wallace *P*	Differentials						
				NDNS	NDLS	NDHS	LDNS	HDNS	LDLS	HDHS
Maternal age	27.652	<.01	<.01	c	d	a	d	bc	e	ab
Gravidity	22.686	<.0001		bc	b	a	d	bcd	cd	a
BMI	20.268	<.0001		a	b	ab	a	ab	b	ab
Mean income per household	14.802	<.01	<.01	a	b	abcd	a	abc	cd	d
Gestational age at enrolment	4.9667	<.01	<.01	d	bc	ab	c	cd	bc	a

N=no, D=drinking, S=smoking, L=low, H=high
Different letters in the columns indicate significant differences between the groups, while common letters indicate that these groups do not differ significantly.

Table 2. Comparison of socioeconomic and drug use variables among drinking and smoking groups

Variable	NDNS	NDLS	NDHS	LDNS	HDNS	LDLS	HDHS	Significance
Employment (N)	773	736	73	742	79	2,318	124	Chi-square (df=6) =134 *P*<.0001
Are employed	341 (44.1)	202 (27.5)	25 (34.3)	343 (46.2)	28 (35.4)	654 (28.2)	33 (26.1)	
Running water (N)	886	875	78	845	88	2,689	126	Chi-square (df=6) =45.25 *P*<.0001
Have running water	753 (87.0)	697 (79.7)	62 (79.5)	730 (86.4)	76 (86.4)	2,167 (80.6)	89 (70.6)	
Toilet (N)	866	875	78	845	88	2,688	126	Chi-square (df=6) =33.58 *P*<.0001
Have toilet	638 (73.7)	559 (63.9)	51 (65.4)	598 (70.1)	58 (65.9)	1,769 (65.8)	73 (57.9)	
Marijuana (N)	880	909	87	868	89	2,705	130	Chi-square (df=6) =306.43 *P*<.0001
Use marijuana	12 (1.4)	85 (9.4)	11 (12.6)	20 (2.3)	6 (6.7)	447 (16.5)	22 (16.9)	
Methamphetamine (N)	879	905	86	868	89	2,705	131	Chi-square (df=6) =168.46 *P*<.0001
Used methamphetamine	2 (0.2)	47 (5.2)	10 (11.6)	13 (1.5)	4 (4.5)	222 (8.2)	17 (13.0)	
Hookah (N)	317	344	28	392	36	1,160	43	Chi-square (df=6) =60.51 *P*=.0000
Used hookah	34 (10.7)	47 (13.7)	5 (17.9)	86 (21.9)	15 (41.7)	296 (25.5)	14 (32.6)	

N in the variable column refers to the number of participants in which the information was available
N=no, D=drinking, S=smoking, L=low, H=high
Data are n (%) unless otherwise stated.

Table 3. Comparison of the pulsatility indices, fetal biometry and birth outcome in the different smoking and drinking groups

Variable	F	Anova *P*	Kruskal Wallace *P*	Differentials						
				NDNS	NDLS	NDHS	LDNS	HDNS	LDLS	HDHS
Uterine artery PI at 20-24 weeks	1.6588	.13	.04	a	a	a	a	a	a	b
Umbilical artery PI at 20-24 weeks	4.9153	<.01	<.01	c	c	bc	c	bc	b	a
Biparietal diameter at 34-38 weeks	2.5866	.02	.04	a	a	a	a	a	a	b
Head circumference at 34-38 weeks	1.8485	.09	.05	a	a	a	a	a	a	b
Femur length at 34-38 weeks	2.4730	.02	.02	ab	ab	ab	a	abc	b	c
Percentile of placental weight	2.7570	.01	.03	b	b	a	bc	bc	bc	e
Birth weight Z-scores	18.488	<.01	<.01	a	c	abcd	b	bcd	d	e
Gestational age at delivery	8.7396	<.01	<.01	a	bc	cd	a	ab	bc	d

N=no, D=drinking, S=smoking, L=low, H=high
Different letters in the columns indicate a significant difference, while common letters indicate that these groups do not differ significantly.

Table 4. Frequency of placental abruption according to a two-tier classification

	No smoking	Smoking only	Total	Significance	No drinking	Drinking only	Total	Significance
N	2,515	3,127	5,642	Chi-square (df=1) =6.86 *P*=.00882	3,439	2,203	5,642	Chi-square (df=1) =0.00 *P*=.96884
Abruption, n (%)	13 (0.52)	36 (1.15)	49 (0.87)		30 (0.87)	19 (0.86)	49 (0.87)	

Table 5. Frequency of placental abruption according to a seven-tier classification

	NDNS	NDLS	NDHS	LDNS	HDNS	LDLS	HDHS	Significance
N	875	907	88	865	89	2,804	136	Chi-square (df=6) =20.02 *P*=.00275
Abruption, n (%)	1 (0.11)	5 (0.55)	0 (0.0)	8 (0.92)	0 (0.0)	35 (1.25)	0 (0.0)	

N=no, D=drinking, S=smoking, L=low, H=high

Table 6: Effects of different variables on the presence of placental abruption		
Continuous data		
Variable	**MWU Z value**	**MWU P value**
Maternal BMI	1.68	0.10
Birthweight Z score	1.40	0.16
Gestational age at enrolment	1.07	0.23
Maternal age	0.283	0.78
Maternal gravidity	-0.20	0.85
Nominal data		
Variable	**ML Chi-square (df=1)**	**ML Chi-square P *v*alue**
Methamphetamine use	9.89	**0.0017**
Hypertension	13.78	**0.0021**
Maternal employment	4.32	**0.038**
Marijuana use	1.63	0.202
Toilet in house	1.28	0.259
Running water in house	0.70	0.403
Hookah pipe use	0.22	0.638
MWU = Mann-Whitney-U; ML = Maximum likelihood		