The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: http://www.tandfonline.com/loi/ijmf20

Causes of stillbirth in a socioeconomically disadvantaged urban Australian population – a comprehensive analysis

Laura Anna Wijs, Esti Charlotte de Graaff, Shalem Leemaqz & Gustaaf Dekker

To cite this article: Laura Anna Wijs, Esti Charlotte de Graaff, Shalem Leemaqz & Gustaaf Dekker (2016): Causes of stillbirth in a socioeconomically disadvantaged urban Australian population – a comprehensive analysis, The Journal of Maternal-Fetal & Neonatal Medicine, DOI: 10.1080/14767058.2016.1265933

To link to this article: http://dx.doi.org/10.1080/14767058.2016.1265933

Accepted author version posted online: 28 Nov 2016.
Published online: 20 Dec 2016.

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE, 2016
http://dx.doi.org/10.1080/14767058.2016.1265933

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Causes of stillbirth in a socioeconomically disadvantaged urban Australian population – a comprehensive analysis

Laura Anna Wijs[a], Esti Charlotte de Graaff[a], Shalem Leemaqz[b] and Gustaaf Dekker[c]

[a]Women and Children's Division, Lyell McEwin Hospital, Robinson Institute, University of Adelaide, Adelaide, Australia; [b]University of Adelaide, Adelaide, Australia; [c]Department of Obstetrics & Gynaecology, University of Adelaide, Adelaide, Australia

ABSTRACT

Introduction: The aim of this paper was to provide an in-depth analysis of all stillbirth causation over a period of 10 years in a busy maternity unit located in a socioeconomically disadvantaged urban area, with an emphasis on overlapping pathology.

Materials and methods: A retrospective analysis of all structurally normal stillbirths in singleton pregnancies born during 2002–2012. The PSANZ stillbirth classification was used; per stillbirth subgroup main risk factors were evaluated.

Results: Out of 130 cases, 43% showed overlapping pathologies. In the remaining 74 (56%) cases, the following single pathologies were found: IUGR 20 (15%), infection 12 (9%), abruption 8 (6%), placental thrombotic pathology 8 (6%), miscellaneous 6 stillbirths (5%), and 20 cases (15%) unexplained. Smoking was a risk factor for stillbirth associated with abruption (OR 3.639), infection (OR 2.271), and thrombotic pathology (OR 2.168). Drug use had an association with (placental) infection (OR 3.598). Obesity showed a significant association with IUGR (OR 3.782) and abruption (OR 9.040). Thrombophilia risk analysis for the overall group of stillbirths showed significant results for Protein S (OR 8.889) and homocysteine >90th centile (OR 2.087).

Conclusions: Overlapping pathology was identified in 43% of stillbirths. Infection, IUGR, and abruption were the most important single cause of stillbirth.

ARTICLE HISTORY
Received 13 September 2016
Revised 7 November 2016
Accepted 24 November 2016

KEYWORDS
Stillbirth; causes; Australia

Introduction

Stillbirth has a disastrous impact on the life of parents [1]. While the general public in Western society may not perceive stillbirth as an important issue, recent research paint a very different picture. In 2015, the rate of third-trimester stillbirths was estimated to be 2.6 million [2].

Detailed analysis of all stillbirth cases is required to identify potentially preventable and/or treatable causes, with the aim to optimize the outcome of subsequent pregnancies and also to provide a degree closure for the parents.

Stillbirth has finally received appropriate attention in the medical literature and also in the lay press. The recent *Lancet* series provided comprehensive reviews on stillbirth and its causation [3–6]. The Northern suburbs of Metropolitan Adelaide provide a relatively rare opportunity to complete an in-depth analysis of stillbirth in a poor but primarily Caucasian population, with in itself good access to health care. Adelaide's Northern suburbs are considered one of the most socioeconomically deprived urban areas of Australia, with high rates of poverty, smoking, drug use, and depression.

Many risk factors are known to be associated with stillbirth, but the final cause of death is not always clear. The current Perinatal Society of Australia and New Zealand (PSANZ) stillbirth classification identifies 11 main categories as causes of perinatal death [7]. The problem with this well established classification is that it does not allow easy classification of those cases with overlapping pathology.

The aim of this in depth analysis is to give an overview of the possible causes and cause-related risk factors of stillbirth in this socioeconomically deprived region, with a particular focus on overlap between recognized major pathophysiologic pathways and their association with individual well-established risk factors.

Materials and methods

During 2002–2012, 177 stillbirths were born at the Lyell McEwin Hospital, University of Adelaide and were subsequently reported to the South Australian

CONTACT Laura Anna Wijs laura.wijs@me.com Women and Children's Division, Lyell McEwin Hospital, Robinson Institute, University of Adelaide, Adelaide, 5005 Australia

Table 1. Demographics of cases and controls.

Variable	Category	Control ($n = 260$) Mean ± SEM *N* (%)	Stillbirth ($n = 130$) Mean ± SEM *N* (%)	*p*
Age		27.48 ± 0.36	27.98 ± 0.51	0.3918
BMI		26.82 ± 0.41	27.98 ± 0.67	0.239
Smoking		70 (27.0%)	35 (27.1%)	1.000
Alcohol use		16 (6.2%)	9 (7.2%)	0.8254
Drug use		14 (5.4%)	12 (9.7%)	0.1489
GBS positive		27 (13.9%)	18 (18.0%)	0.3903
Fetal sex	Male	145 (55.8%)	61 (47.7%)	Ref
	Female	115 (44.2%)	67 (52.3%)	0.1067
Gestation		38.90 ± 0.11	30.68 ± 0.66	0
Birth weight		3313.70 ± 33.79	1738.47 ± 112.31	0
Birth length		49.34 ± 0.15	40.59 ± 1.00	0
Customized centile		46.44 ± 1.80	25.16 ± 2.64	0

BMI: Body Mass Index, GBS: Group B streptococcus.

Pregnancy Outcome Unit. After excluding 47 terminations of pregnancy for chromosomal/congenital anomalies, 130 structurally normal stillbirths were available for this analysis.

Medical case notes, histology, and autopsy reports were reviewed for all cases. Where appropriate, results were compared with data from the South Australian Perinatal Database. Thrombophilia findings (factor V Leiden, prothrombin gene, MTHFR, Protein S deficiency, and Homocysteine) in cases were compared with Lyell McEwin patients with a totally normal pregnancy outcome (gestational age >37 weeks, no preeclampsia, no SGA, no Gestational hypertension, no GDM) recruited in the SCOPE study [8].

For the remaining variables (e.g. drug and alcohol use), for which there were no statewide data available, controls were included in this study by matching all cases with women with life birth of similar parity [9]. The first woman giving birth before and after the index case of the same parity was used as control (Table 1).

In order to identify SGA cases, customized centiles (for maternal ethnicity, height, weight, fetal sex) were used [10,11].

Variables used in this analysis

Fetal data

Birth weight, fetal sex, and gestational age were recorded. Customized centiles were calculated for every birth.

Laboratory variables

Presence of Group B Streptococcus (GBS) prior to labor, thyroid function tests, glucose challenge test (GCT), GTT, HbA1c, CRP, bacterial cultures (low vaginal swab, urine, placental swab, fetus), Toxoplasmosis serology, viral infections (CMV serology, PCR, histopathology), prothrombin gene, factor V Leiden, MTHFR 677CT and MTHFR 1298AC polymorphism's, lupus anticoagulant, cardiolipin antibodies, protein S, fasting homocysteine level, and bile acids.

Definitions used in this analysis

Stillbirth

Fetal death occurring at ≥20 weeks and/or a birth weight of ≥400 grams, if gestational age is missing.

MTHFR

Patients with the MTHFR polymorphism were split in three groups: wild-type, heterozygote abnormal (i.e. 677 CT or 1298 AC), or homozygote (i.e. 677 TT or 1298 CC)/compound heterozygous; 677 CT/1298 AC) abnormal.

Protein S

Protein S deficiency is defined as a protein S level <55% on two occasions, at least six weeks postpartum; <55% equates to -2 SD or <2.5th centile of the normal population.

Homocysteine

A fasting homocysteine level with a cutoff of ≥9.0 was considered abnormal; ≥ 9 μmol/L equates to >90th centile for the normal non-pregnant female population [12].

Feto-placental infection

The following histological findings: acute chorioamnionitis, chorionitis, villitis, funisitis, and infection confirmed by multiple positive cultures in placenta and fetus or a combination of one of these.

Placental thrombotic pathology

Infarction, massive (inter)villous fibrin deposition, decidual vessel thrombosis, fetal thrombotic vasculopathy, fetal vessel thrombosis.

Abruption

Either defined clinically or by histologic examination, i.e. retro-placental hemorrhage.

Systemic infections

Syphilis, CMV, parvovirus, toxoplasmosis, rubella, and herpes simplex.

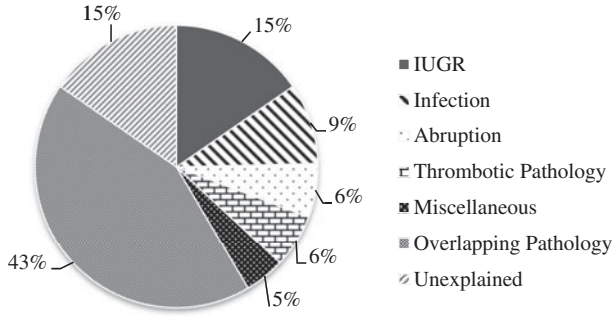

Figure 1. Distribution of possible causes of stillbirth.

Unexplained stillbirth

Stillbirths were considered unexplained when the baby was normally grown, the placenta showed no sign of infection and all aforementioned tests performed (except the thrombophilias) were negative.

Results

The main demographics of cases and controls are presented in Table 1.

Regarding the 130 structurally normal stillbirths, 0.5% of the total number ($N = 26.387$) of births within this decade was stillborn.

Possible causes of stillbirth could be divided into the following main groups: Intra Uterine Growth Restriction (IUGR), infection (e.g. viral and bacterial placental infection and/or inflammation), abruption, thrombotic pathology, miscellaneous group (e.g. maternal Diabetes Mellitus, Warfarin associated hemorrhage etc.), and a combination of any of these and unexplained death.

Figure 1 presents a distribution of most likely causes, also illustrating the 43% of cases with overlapping pathologies.

An overview of the main categories of stillbirth and the associated overlapping pathologies is seen in Table 2. Note that the numbers do not add up to 100%, as these tables do not show the exact number of cases, but the frequency of certain pathologies found within each group.

IUGR

IUGR was detected in 61 of the 130 stillbirths (46.9%).

The distribution of the customized growth centile within the cases and controls group is presented in Figure 2; the two curves show a marked and significant discrepancy associated with birth weight centiles <10th.

Using univariate analysis, no significant difference was found between smoking (21.3% of the IUGR stillbirth cases versus 27% of the controls), with also no differences for alcohol and/or drugs when comparing this subgroup with the controls. An increasing BMI was found to be significantly associated with IUGR (p(0).0184). Especially being morbidly obese (BMI ≥40) increased the risk of delivering a growth-restricted stillborn baby (OR 3.782, 95% CI 1.034–12.871). Of the 61 cases with IUGR, 7% were term stillbirths with a morbidly obese mother.

Table 2. Overlapping pathologies within the different subgroups.

	IUGR ($n = 61$)	Infection ($n = 42$)	Thrombotic pathology ($n = 35$)	Abruption ($n = 23$)
N/A	20 32.8%	12 28.6%	8 22.9%	8 34.8%
IUGR		13 31.0%	18 51.4%	10 43.5%
Infection	16 26.2%		9 25.7%	2 8.7%
Thrombotic pathology	18 29.5%	9 21.4%		4 17.4%
Abruption	10 16.4%	2 4.8%	3 8.6%	
Pre-PROM	10 16.4%	11 26.2%	- 0.0%	3 8.6%

N/A: no additional pathology; IUGR: intra uterine growth restriction; Pre-PROM: Preterm premature rupture of membranes.

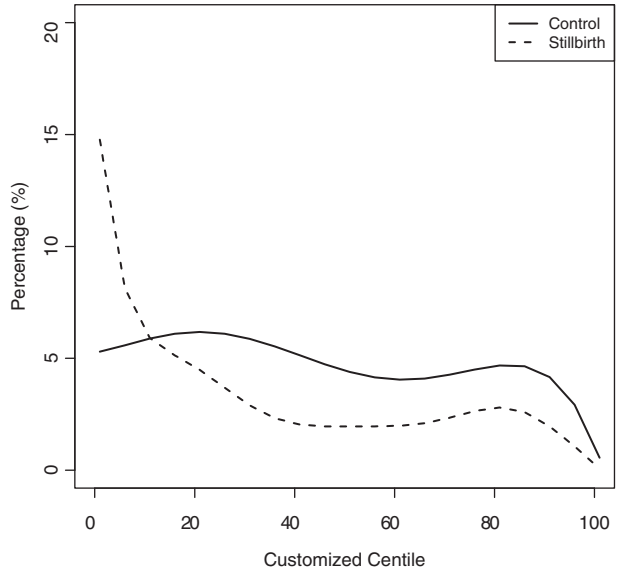

Figure 2. Distribution of customized centiles of cases and controls.

Infection

In 42 of the 130 stillbirths (32.3%), infection was detected.

In our analysis, five stillbirths were found to have a systemic viral infection, three CMV – each showing additional features – and 2 Parvo infections.

In 37 cases, placental histology and/or microbiology results indicated bacterial infection and/or placental inflammation; 32% showed chorioamnionitis, 30% showed a combination of chorioamnionitis and funisitis, 30% showed heavy growth of microbes and/or signs of fetal septicemia, 5% showed chorionitis, and 3% showed villitis.

Of the 37 cases with an infectious response or placental inflammation, 28 (76%) were tested positive for a microorganism; 6 (21%) of these were proven to be GBS, 20 (71%) feto-placental infections were likely caused by other microorganisms than GBS, such as *Escherichia coli*, *Enterococci*, *Streptococcus milleri*, gram-negative Bacilli, *Ureaplasma urealyticum*, *Haemophilus influenzae*, and *Staphylococcus aureus*. Two cases (7%) had a proven combination of GBS and another organism. The remaining 9 (24%) cases were tested negative for any microorganism.

There was no significant difference in the rates of positive low vaginal GBS cultures (13.9% controls vs. 17.8% stillbirth cases; OR 1.34; 95% CI 0.69–2.57).

Within all stillbirths in this study, 44 were term or post-term deliveries. Fifteen of these (34%) showed a placental infection or inflammation as one of the findings at post mortem examination.

Using univariate analysis both smoking (OR 2.271, 95% CI 1.039–4.691) and drug use (OR 3.598, 95% CI 1.050–10.959) showed to have a significant correlation with feto-placental infection. Increased BMI was not associated with placental infection.

Placental thrombotic pathology

In 35 of the 130 stillbirth cases (26.9%), placental thrombotic pathology was identified.

Most of the thrombotic pathologies found, consisted of either fetal thrombotic vasculopathy or infarctions. Details on thrombophilia findings are provided in Table 3.

Within this group of 35 index cases with thrombotic pathology, 31% were reported as smokers, which has a significant relation with the thrombotic pathologies found (OR 2.168, 95% CI 0.959–4.598).

Placental abruption

Abruption was identified in 23 of the 130 stillbirths (17.7%).

About 43% of the stillbirths caused by abruption were smokers (OR 3.639, 95% CI 1.428–8.986), whereas alcohol and drug use showed no correlation with abruption. Increasing BMI was significantly associated with placental abruption (p(0).0031). This risk was seen particularly in the morbidly obese women (OR 9.040, 95% CI 2.031–36.895).

Thrombophilias

Table 3 provides details on thrombophilias identified in stillbirth, differentiating between several placental pathologies.

MTHFR and homocysteine

The maternal MTHFR genotypes (heterozygous, homozygous, compound heterozygous) had no association with stillbirth (OR 0.8799, 95% CI 0.5504 –1.407). Of the 85 patients in which homocysteine was measured, 16 patients had hyperhomocysteinemia (cut off >90th centile); OR 2.087, 95% CI 1.166 – 3.734). Only five cases were tested positive for antiphospholipids (e.g. Lupus Anticoagulans ($N = 1$) and Cardiolipin ($N = 4$)) within this study.

Unexplained stillbirth

In this 10-year cohort, 20 (15%) stillbirths remained unexplained after complete examination. Unexplained stillbirths were mostly late pregnancies (e.g. ≥28 weeks), only three of the unexplained stillbirths were born under 28 weeks of gestation; 10 babies were term stillborn.

Discussion

This overview of 10 years of stillbirth in a busy maternity service located in a very socioeconomically

Table 3. Overview of thrombophilic disorders within the groups.

(controls: $n = 988$)	All cases	IUGR	Thrombotic pathology	Abruption
Factor V Leiden (4.4%)	6.9%	7.3%	3.0%	13.6%
	OR: 1.607	OR: 1.702	OR: 0.6781	**OR: 2.997**
	CI: 0.7362–3.509	CI: 0.5879–4.926	CI: 0.0904–5.082	**CI: 1.002–8.958**
Prothrombin (2.5%)	3.4%	5.4%	3.0%	0.0%
	OR: 1.373	OR: 2.176	OR: 1.201	OR: 0.8769
	CI: 0.4691–4.017	CI: 0.6364–7.439	CI: 0.1578–9.147	CI: 0.0516–14.889
Protein S deficiency (2.5%)	18.8%	14.7%	11.1%	6.7%
	OR: 8.889,	**OR: 6.641**	**OR: 4.815**	OR: 2.751
	CI: 4.229–18.686	**CI: 2.373–18.585**	**CI: 1.050–22.082**	CI: 0.3480–21.756
Overall (9.4%)	28.2%	25.6%[a]	17.1%[a]	20.3%[a]

Bold values indicate the significant results.
[a]Percentage within the subgroup.

disadvantaged urban environment with primarily Caucasian patients identified IUGR, infection, abruption, and thrombotic pathology as the main causes of stillbirth. Importantly these data clearly indicate that how difficult it is to decide on a definitive cause of a particular stillbirth; in 43% of stillbirths, there were at least two major types of pathology.

IUGR has a well-known association with stillbirth; this association was again clearly seen in the current study. In historical classification systems, stillborn with IUGR were often classified as unexplained stillbirths [13]. Ever since IUGR was recognized as a major cause of death, the number of unexplained stillbirths has declined dramatically [14,15].

It is also important to emphasize that close to 60% of IUGR cases had major additional pathology leading to the stillbirth. During pregnancy, knowledge of the fetal growth trajectory gives important information on its wellbeing and the development of the placenta [16]. Recognizing actual IUGR in a clinical setting is a major challenge in obstetrics. The recent renewed interest on the Doppler cerebroplacental ratio in the management of term IUGR may turn out to be of great clinical importance for that matter. Obese patients have a much higher risk of IUGR-associated stillbirth. However, ultrasound is notoriously difficult in morbidly obese mothers, making obesity an ever-increasing problem also from a stillbirth perspective.

Infection is a common cause of stillbirth worldwide [17]. In a comprehensive review by Khong on placental findings in case of stillbirth, the relation between placental infection and stillbirth is described [18]. Chorionitis and villitis are more likely to be ascribed to a nonspecific inflammatory response of the fetus on the placenta rather than an infection, whereas the combination of chorioamnionitis and funisitis is more likely to reflect bacterial infection as cause of death [19]. Villitis has a proven importance in stillbirth [20]. Varli et al. found that chronic villitis, acute chorioamnionitis and villous immaturity are common in term stillbirths, whereas no association was found for funisitis. We found similar results within our term stillbirths. In some cases, there were clinical signs of infection, but no microorganisms were detected, possibly due to patients receiving antibiotics during pregnancy or labor.

In contrast to the study by Monari et al. [21], no differences were found between cases and controls regarding positive low vaginal GBS cultures and the risk of stillbirth. Although GBS is a well-established risk factor for preterm birth and neonatal sepsis, GBS did not have a significant role in stillbirth causation in this particular cohort [22,23].

In one of the publications in the excellent "Stillbirth Series" in *The Lancet*, Flenady et al. found that of all pregnancy disorders, abruption is one of the strongest risk factors for stillbirth [24]. Other research found that there is an 8.9-fold increased relative risk of stillbirth associated with partial placental abruption [25]. Although our study did not identify abruption as the most common cause of stillbirth, it did demonstrate its importance with an overall incidence of 17%. Additionally, abruption and IUGR seemed to have a correlation. Almost 44% of the cases with an abruption were also growth restricted. Supporting this finding, previous research also showed a strong correlation between severe IUGR and placental abruption [26]. In contrast, this same study on risk factors of placental abruption suggested an association between preterm premature rupture of membranes (Pre-PROM) and placental abruption, data from the current study did not support this association.

A meta-analysis on thrombotic pathology and the risk of stillbirth showed that several thrombotic disorders have a correlation with stillbirth [27]. In our analysis, 28.2% of cases had a thrombophilia compared to 9.4% in patients with a normal pregnancy outcome in the SCOPE study (OR 3.8; 95% CI 2.47–5.92). In particular, protein S deficiency was significantly more common. It needs to be emphasized that the measurement of protein S deficiency is notoriously difficult; however, all these cases were tested twice at least 6 weeks post-partum and the cutoff was strict ($<$ 55%). Our results also show a significant correlation between factor V Leiden and abruption [28].

In this study, we opted not to include heterozygosity for one of the MTHFR polymorphisms as a thrombophilia. However, also carrying two mutated alleles was not more common amongst the cases (21.2%) compared with the controls (19.1%).

Homocysteine is a pro-inflammatory and pro-thrombotic amino acid influenced by many factors, including the MTHFR genotype, smoking, coffee, diet, pregnancy, and stress. The percentage of cases with a homocysteine $>$90th centile was significantly increased – indicating that in this study the thrombophilia aspects of this pathway were more relevant than possible epigenetic changes [27].

Smoking was found be significantly more common in patients with different types of stillbirth-associated pathology. This is in line with existing literature showing a similar clear correlation between smoking and abruption [29]. Even though we could observe a decline in the number of smokers over this decade, the persisting high rate of smoking in this particular

environment suggest that further smoking cessation would result in a detectable drop in stillbirths.

According to O'Leary et al. heavy drinking increases the risk of having stillbirth [30]. However, this association has not been found for more moderate drinking. Contributing to findings in former research, alcohol usage was not found to be significant for adverse pregnancy outcome in the prospective SCOPE cohort [31]. In all these studies, including the current study, we cannot exclude the possibility of significant underreporting of excessive alcohol use during pregnancy. The same issue may affect the data on the effects of drug use. In our study, drug use only had a significant association with (placental) infection. In 2005, Kennare et al. investigated drug use during pregnancy in South Australia and concluded that outcomes often cannot be explained by substance use alone [32]. We see the same pattern in our study population. However, it should be noted that several recent studies found drug use to increase the risk for stillbirth [33,34].

Obesity is a truly major health problem in the socioeconomically disadvantaged Northern suburbs of Adelaide. In this study, increasing BMI was found to be a risk factor for IUGR and abruption. Former research showed the same association between obesity and fetal growth disorders [35]. Though, to our knowledge, the association between obesity and abruption has not been previously described.

An important limitation of this study was due to the fact that notwithstanding existing guidelines, the stillbirth analysis was not completed in a consistent way and often quite incomplete. The high numbers of missing values on certain laboratory tests make it hard to assess the effect of underlying disorders (e.g. the thrombophilia's). Another well-known problem is that parents often decline autopsy, leaving the placental histology report as the main source. A second limitation was the relatively low numbers even in this cohort of 10 years in a busy maternity unit; in particular, analysis in different subsets was hampered by the limited number of cases in the different categories of underlying pathology.

Summary

The main causes of stillbirth in this socioeconomically disadvantaged population were growth restriction, infection, thrombotic pathology, and abruption, but importantly 43% of the cases had overlapping pathology. The epidemic of obesity is the number one potentially preventable risk factor for stillbirth. Increasing BMI is a risk factor for IUGR, abruption, and stillbirth. To our knowledge, the association between obesity and abruption has not been previously identified.

The high percentage of overlap supports a comprehensive protocol to be applied for all cases of stillbirth, also in these cases where an initial direct cause appears to be obvious. Future classifications should allow identification of overlapping main pathophysiological pathways that would allow better understanding of the overall chain of events leading to stillbirth.

Disclosure statement

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

References

1. Heazell AEP, Siassakos D, Blencowe H, et al. Stillbirths: economic and psychosocial consequences. Lancet 2016;387:604–16.
2. Lawn JE, Blencowe H, Waiswa P, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet 2016;387:587–603.
3. Flenady V, Wojcieszek AM, Middleton P, et al. Stillbirths: recall to action in high-income countries. Lancet 2016;387:691–702.
4. De Bernis L, Kinney MV, Stones W, et al. Stillbirths: ending preventable deaths by 2030. Lancet 2016;387:703–16.
5. Flenady V, Middleton P, Smith GC, et al. Stillbirth: the way forward in high-income countries. Lancet 2011;377:1703–17.
6. Froen JF, Cacciatore J, McClure EM, et al. Stillbirth: why they matter. Lancet 2011;377:1353–66.
7. Twenty-sixth Report of Maternal, Perinatal and Infant Mortality committee. Adelaide, South Australia: Government of South Australia, SA health. 2011.
8. Zhou A, Dekker GA, Lumbers ER, et al. The association of maternal *ACE A11860G* with small for gestational age babies is modulated by the environment and by fetal sex: a multicentre prospective case–control study. Mol Hum Reprod 2013;19:618–27.
9. de Graaff EC, Wijs LA, Leemaqz S, et al. Risk factors for stillbirth in a socio-economically disadvantaged urban Australian population. J Matern Fetal Neonatal Med 2017;30:17–22.
10. Gardosi J. Customised assessment of fetal growth potential: implications for perinatal care. Arch Dis Child Fetal Neonatal Ed 2012;97:F314–F317.
11. van Eerd EA, Roex AJ, Nikpoor P, et al. Adverse perinatal outcome and maternal risk factors in population versus customized defined SGA babies. J Matern Fetal Neonatal Med 2012;25:369–73.
12. Fenech M, Aitken C, Rinaldi J. Folate, vitamin B12, homocysteine status and DNA damage in young Australian adults. Carcinogenesis 1998;19:1163–71.

13. Frøen JF, Gardosi JO, Thurmann A, et al. Restricted fetal growth in sudden intrauterine unexplained death. Acta Obstet Gynecol Scand 2004;83:801–7.
14. Gardosi J, Kady SM, McGeown P, et al. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. BMJ 2005;331:1113–7.
15. Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. AJOG 2011;204:288–300.
16. Baschat A. Fetal responses to placental insufficiency: an update. BJOG 2004;11:1031–41.
17. Goldenberg RL, McClure EM, Saleem S, et al. Infection-related stillbirths. Lancet 2010;375:1482–90.
18. Khong. Y. The placenta in stillbirth. Curr Diag Pathol 2006;12:161–72.
19. Pinar H, Goldenberg RL, Koch MA, et al. Placental findings in singleton stillbirths. Obstet Gynecol 2014;123: 325–36.
20. Varli I H, Petersson K, Kublickas M, et al. Both acute and chronic placental inflammation are overrepresented in term stillbirths: a case-control study. Infect Dis Obstet Gynecol 2012;2012:Article ID. DOI: 10.1155/2012/293867. 293867.
21. Monari F, Gabrielli L, Gargano G, et al. Fetal bacterial infections in antepartum stillbirth: a case series. Early Hum Dev 2013;89:1049–54.
22. Kessous R, Weintraub AY, Sergienko R, et al. Bacteruria with group-B streptococcus: is it a risk-factor for adverse pregnancy outcomes? J Matern Fetal Neonatal Med 2012;25:1983–6.
23. Clifford V, Garland SM, Grimwood K. Prevention of neonatal group B streptococcus disease in the 21st century. J Paediatr Child Healt 2012;48:808–15.
24. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet 2011; 377:1331–40.
25. Ananth CV, Berkowitz GS, Savitz DA. Placental abruption and adverse perinatal outcomes. JAMA 2003;282: 1646–51.
26. Budde MP, De Lange TE, Dekker GA, et al. Risk factors for placental abruption in a socia-economically disadvantaged region. J Matern Fetal Neonatal Med 2007;20:687–93.
27. Rey E, Kahn SR, David M, et al. Thrombophilic disorders and fetal loss: a meta-analysis. Lancet 2003;361:901–08.
28. Kupferminc MJ. Thrombophilia and pregnancy. Reprod Biol Endocrinol 2003;1:111.
29. Tikkanen M, Nuutila M, Hiilesmaa V, et al. Clinical presentation and risk factors of placental abruption. Acta Obstet Gynecol Scand 2006;85:700–05.
30. O'Leary C, Jacoby P, D'Antoine H, et al. Heavy prenatal alcohol exposure and increased risk of stillbirth. BJOG 2012;119:945–52.
31. McCarthy FP, O'Keeffe LM, Khashan AS, et al. Association between maternal alcohol consumption in early pregnancy and pregnancy outcomes. Obstet Gynecol. 2013;122:830–7.
32. Kennare R, Heard A, Chan A. Substance use during pregnancy: risk factors and obstetric and perinatal outcomes in South Australia. Aus N Z J Obstet Gynaecol 2005;45:220–5.
33. Varner MW, Silver RM, Hogue CJ, et al. Association between stillbirth and illicit drug use and smoking during pregnancy. Obstet gynecol 2014;123:113–25.
34. Viteri OA, Mendez-Figueroa H, Pedroza C, et al. Relationship between self-reported maternal substance abuse and adverse outcomes in the premature newborn. Am J Perinatol 2016;33:165–71.
35. Marsh CA, Hecker E. Maternal obesity and adverse reproductive outcomes: reducing the risk. Obstet Gynecol Surv 2014;69:622–8.