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ORIGINAL ARTICLE

Causes of perinatal deaths in Australia: Slow progress in the preterm period

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Aim: The majority of perinatal deaths occur in the preterm period; however, current approaches predominantly focus on prevention in the term period. Reducing perinatal deaths in the preterm period is, therefore, key to reducing the rates of perinatal death overall in Australia. The aim was to understand the classifications of causes of preterm stillbirth and neonatal death in Victoria over time and by gestation.

Materials and methods: Retrospective study using state-wide, publicly available data. All births in Victoria between 2010 and 2018 included in the Victorian Perinatal Data Collection, excluding terminations of pregnancy for maternal psychosocial indications, were studied. Differences in causes of preterm perinatal mortality gestation group and over time were determined.

Results: Out of 7977 perinatal deaths reported, 85.9% (n = 6849) were in the preterm period. The most common cause of preterm stillbirths was congenital anomalies (n = 1574, 29.8%), followed by unexplained antepartum deaths (n = 557, 14.2%). The most common cause of preterm neonatal death was spontaneous preterm birth (sPTB; n = 599, 38.2%), followed by congenital anomalies (n = 493, 31.4%). The rate of preterm stillbirths due to hypertension (−14.9% (95% CI −27.1% to −2.7%; P = 0.02)), maternal conditions (−24.1% (95% CI −44.2% to −4.0%; P = 0.03)) and those that were unexplained (−5.4% (95% CI −9.8% to −1.2%; P = 0.02)) decreased per annum between 2010 and 2018. All other classifications did not change significantly over time.

Conclusion: Prevention of congenital anomalies and sPTB is critical to reducing preterm perinatal mortality. Greater emphasis on understanding causes of preterm deaths through mortality investigations may reduce the proportion of those considered 'unexplained'.

KEYWORDS

cause of death, neonatal death, perinatal death, preterm, stillbirth,

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INTRODUCTION

The loss of a baby is a devastating outcome with far-reaching impacts on individuals, families and communities.[1,2] Current approaches to reducing perinatal death focus predominantly on care in the term period.[3] The benefits of these targeted approaches are beginning to be realised, and the proportion of stillbirths occurring in the term period has decreased from 25% to 15% over the past two decades in Australia.[4] These same gains, however, have not been observed in the preterm period (before 37 weeks' gestation). Of the 1256 babies who were stillborn in Australia in 2018, 90% of them (*n* = 1136) were born at <37 weeks' gestation, and 71% (*n* = 889) were born before 28 weeks' gestation.[5] Hence, while term stillbirths have reduced, the overall stillbirth rate has remained at approximately six babies per day for over a decade.[5] Reducing stillbirth in the preterm period is, therefore, key to reducing the rates of stillbirth overall in Australia. Similarly, the rate of neonatal death (NND) in Australia has remained stagnant for over a decade, with roughly two babies a day dying in the neonatal period, many of which are the result of prematurity.

Together, both stillbirths and NND make up perinatal deaths; however, epidemiological studies of preterm perinatal mortality tend to focus on either stillbirth or NND, despite them sharing common pathways.[6,7] Furthermore, there are several challenges in understanding trends in preterm perinatal death. Firstly, national-based reporting shows that causes of death in the preterm period differ by gestation;[5] however, the significance of these differences is not well understood. National data sets also do not delineate terminations of pregnancy (TOP) >20 weeks' gestation, which clouds our understanding of the key causes of perinatal death.[8] Over the past decade, clinical care, frequency of perinatal autopsy[9,10] and the obstetric risk profile of women giving birth in Australia have changed.[11,12] It is unknown, however, whether the causes of preterm perinatal death between gestations have changed over time in relation to these changing factors.

This study aims to address these limitations, with a goal to identify future directions to reduce preterm perinatal death. Using detailed Victorian data, we present the differences in causes of perinatal death, delineating between stillbirths and NND, by preterm birth gestational groups and over time between 2010 and 2018.

MATERIALS AND METHODS

This was a population-based retrospective cohort study of all births in Victoria. We extracted data from the publicly available Victoria's Mothers, Babies and Children's reports, reporting on all births and deaths from 2010 to 2018. As part of the Victorian Perinatal Data Collection (VPDC), these reports include data for all births and perinatal deaths reported to the Consultation Council on Obstetric and Paediatric Mortality and Morbidity (CCOPMM), the state's independent advisory body on maternal, perinatal, and paediatric mortality. Once reviewed by CCOPMM, data are deidentified and published annually.[13,14]

TABLE 1 Perinatal deaths by gestation group between 2010 and 2018[†]

	Proportion	Rate per 1000 births
Stillbirths	***n* = 4656**	***n* = 703 525**
Extremely preterm (<28 weeks)	2791 (59.9%)	3.97
Very preterm (28–31^{+6} weeks)	478 (10.3%)	0.68
Moderate-late preterm (32–36^{+6} weeks)	637 (13.7%)	0.91
Term (37+ weeks)	750 (16.1%)	1.07
Total		6.62
NND	***n* = 1946**	***n* = 703 525**
Extremely preterm (<28 weeks)	1267 (65.1%)	1.80
Very preterm (28–31^{+6} weeks)	114 (5.9%)	0.16
Moderate-late preterm (32–36^{+6} weeks)	187 (9.6%)	0.27
Term (37+ weeks)	378 (19.4%)	0.54
Total		2.77

†Perinatal deaths due to TOP for MPI are excluded.

We extracted data for total births, live births and perinatal deaths; stillbirths (>20 weeks' gestation or a weight ≥400 g, if gestation was unknown), and NND (death of a liveborn baby within 28 days of birth) occurring in the preterm period (<37 weeks' gestation) per year. Preterm births were classified according to World Health Organisation (WHO) standard gestational groups, as occurring at <28 weeks (extremely preterm), 28–31^{+6} weeks (very preterm) or 32–36^{+6} weeks (moderate-late preterm) gestation.[15]

We extracted causes of stillbirth and NND, determined according to the Perinatal Society of Australia and New Zealand Perinatal Death Classification (PSANZ-PDC) from the publicly available reports[8] (*please see Appendix 1 for classifications)* for each gestational group and excluded TOP for maternal psychosocial indications (MPI). TOP due to congenital anomaly and other maternal conditions remained included. We tabulated the PSANZ-PDC for stillbirths and NNDs for each preterm group. Differences in proportions were compared using a χ^2 test. Finally, rates of classified cause of perinatal deaths per 1000 births were tabulated by year. Changes in the rates over time were determined by computing the natural logarithms of the rates before performing log-linear regression. Coefficients and 95% CIs were then exponentiated to determine percentage changes. All analyses were undertaken using StataCorp 12.IC. A *P*-value <0.05 (two-tailed) was determined to be statistically significant.

As we accessed publicly reported data, ethical approval was not required and had an exemption from Monash University Human Research Ethics Committee.

RESULTS

A total of 7977 perinatal deaths were reported between 2010 and 2018 in Victoria. After excluding TOP for MPI (n = 1375), 84% (n = 3906) of stillbirths and 80.6% (n = 1945) of NNDs were in the preterm period. For both preterm stillbirths and NND, majority occur in the extremely preterm period, while the least occur in the very preterm period (Table 1). The overall rate of preterm stillbirth was 5.55 per 1000 births, and the rate of preterm NND was 2.23 per 1000.

Cause of preterm stillbirths and NND

The classifications of stillbirths and NND by gestational group are presented in Figure 1.

Congenital anomalies

Congenital anomalies were the most common category of preterm stillbirth (40.3%) and the second most common category of preterm NND (31.4%). Preterm stillbirths due to congenital anomaly were most common in the extremely preterm period (45.4%) and decreased with increasing gestation (34.9% very preterm and 22.1% of moderate-late preterm; $P < 0.001$). In contrast, they were more common in the moderate-late preterm NND (66.3%) compared to earlier gestation groups (26.1% in the extremely preterm period and 34.2% of very preterm; $P < 0.001$).

Spontaneous preterm birth

Deaths due to spontaneous preterm birth (sPTB) were the most common cause of death for NND (38.2%) and decreased with increasing gestation. In contrast, 11.5% of preterm stillbirths were classified as sPTB. sPTB was most common in the extremely preterm groups (45.2% for NND and 15.7% for stillbirth) when compared to later gestations (14.0% for very preterm NND and 5.9% for moderate-late preterm NND ($P < 0.001$) and 1.1% for both very preterm and late preterm stillbirths ($P < 0.001$)).

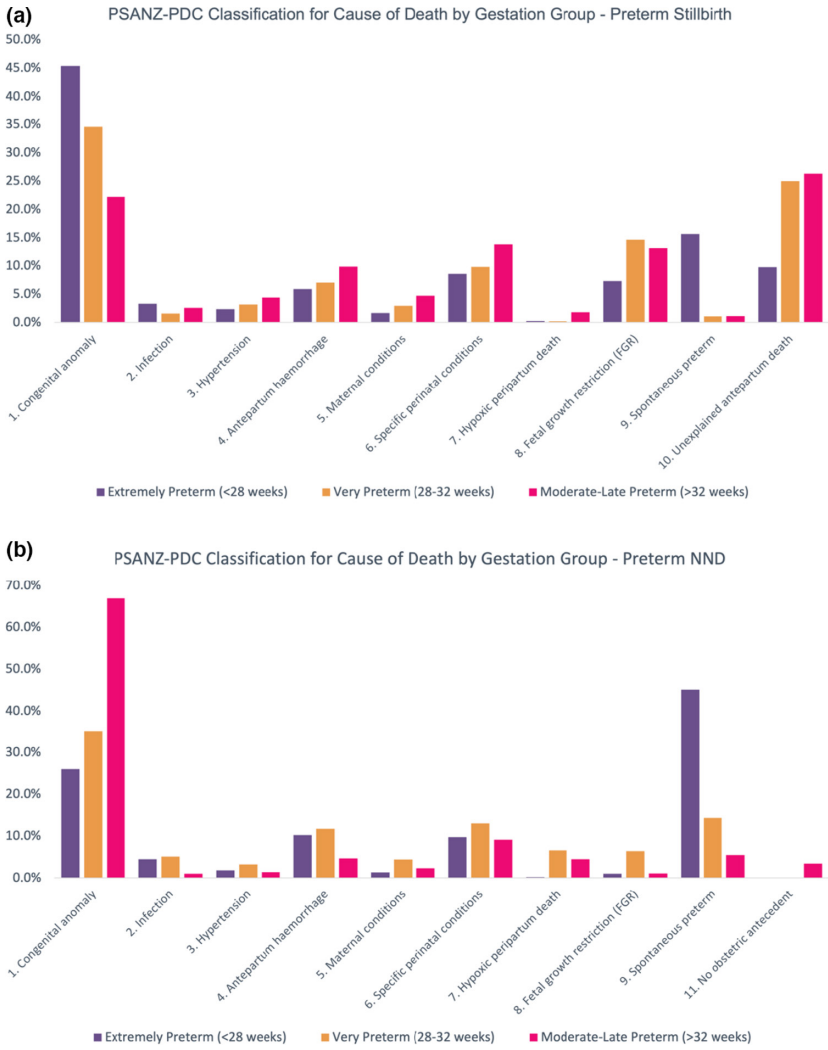

FIGURE 1 PSANZ-PDC cause of stillbirth (a) and neonatal death (NND) (b) by gestation group. Perinatal deaths due to terminations of pregnancy (TOP) for Maternal Psychosocial Indications (MPI) are excluded.

Unexplained antepartum death

'Unexplained antepartum death' was the second most frequent category of preterm stillbirth (14.2%), and the proportion of these increased with increasing gestation from 9.7% in the extremely preterm group to 24.7% very-preterm and 26.4% in the moderate-late preterm period ($P < 0.001$).

Specific perinatal conditions

Specific perinatal conditions, which include birth trauma, uterine abnormalities, twin-twin transfusion, antepartum cord complications and more, made up 9.5% of all preterm stillbirths and were the third most common category attributed to preterm NND (10.1%). Regarding stillbirths, the frequency of specific perinatal conditions went from 8.5% of extremely preterm to 9.8% of very preterm and 13.7% in the moderate-late preterm period ($P < 0.001$). Regarding NND, specific perinatal conditions made up 9.9% and 9.6% of extremely preterm and moderate-late preterm NND respectively, compared to 14.0% of very preterm NND ($P = 0.36$).

Fetal growth restriction

Fetal growth restriction (FGR) was assigned as the cause of death for 9.1% of all preterm stillbirths and 1.4% of preterm NNDs overall. FGR was least common in extremely preterm stillbirths (7.3%) when compared with very preterm (14.4%) and moderate-late preterm (13.2%) ($P < 0.001$). In contrast, 1.0% of NND in the extremely preterm period and 1.1% in the moderate-late preterm period were classified as FGR compared to 6.1% in the very preterm period ($P < 0.001$).

Other causes of death

Antepartum haemorrhage (APH) was assigned as the cause of 9.8% preterm NNDs and 6.7% of preterm stillbirths. The frequency of APH increased with increasing gestation of stillbirth, from 5.9% extremely preterm to 7.1% very preterm and 9.9% moderate-late preterm ($P = 0.001$). In contrast, APH was more common in extremely preterm NND (10.3%) and very preterm NND (12.3%) compared to moderate-late preterm NND (5.4%) ($P = 0.07$). Perinatal deaths due to infection, hypertension, maternal conditions and hypoxic peripartum death were the least common categories for both stillbirth (8.6% total) and NND (8.7% total). The proportion of these categories increased with increasing gestation for stillbirths; however, infection was more common in the extremely preterm group. But for NND, these classifications were all more common in the very preterm period.

Causes of death over time

Finally, the rate of each classification of preterm stillbirth and NND overtime is presented in Table 2. The rate of preterm stillbirths due to hypertension (−14.9% (95% CI −27.1% to −2.7%; $P = 0.02$)), maternal conditions (−24.1% (95% CI −44.2% to −4.0%; $P = 0.03$)) and those that were unexplained (−5.4% (95% CI −9.8% to −1.2%; $P = 0.02$)) decreased per annum between 2010 and 2018. No other classifications changed significantly over time.

DISCUSSION

Overall, we found that most preterm perinatal deaths occur prior to 28 weeks' gestation. The most common causes of perinatal deaths overall were attributed to CA, unexplained fetal death and sPTB; however, their proportions differed by both gestation group and between stillbirths and NNDs. Finally, we also observed a significant decrease in stillbirths due to hypertension, maternal conditions and unexplained antepartum deaths over the study period.

Almost half of preterm stillbirths and one-third of NNDs were classified as congenital anomalies. Rates of preterm perinatal deaths due to congenital anomaly remain unchanged despite recent improvements in and access to non-invasive prenatal testing. Although reported congenital anomalies in early pregnancy have increased across Victoria over the study period,[16] changes to the hierarchy of classification of congenital anomalies in the PSANZ-PDC may have cancelled out a potential rise due to diagnoses. Before 2017, if a congenital anomaly was present, it was classified as the cause of death, whereas now it is classified only if the anomaly is determined to be the cause of death. There are multiple risk factors that increase the likelihood of a baby having a congenital anomaly, including advanced maternal age, high BMI (>35 kg/m^2), nulliparity, maternal country of birth, pre-gestational diabetes and exposure to environmental factors and infections (such as syphilis and rubella).[17] Strategies to mitigate the risk of congenital anomalies, including supplementation with folic acid to reduce neural tube defects and ensuring that women are vaccinated for infections before pregnancy, remain important. This highlights the importance of pre-conception planning and counselling; however, national estimates indicate that as many as 40% of all pregnancies are unintended, which makes prevention of congenital anomalies a challenge.[18]

It is well recognised that preterm stillbirth and preterm NND share common pathways.[6,7] We observed that sPTB was indicated in more than 15% of stillbirths and almost half of NNDs occurring in the extremely preterm period and that the rates of perinatal deaths due to sPTB have remained stagnant. Interventions aimed at sPTB prevention should be prioritised to reduce perinatal deaths and include midwifery continuity-of-care, screening for lower genital tract infections, zinc supplementation, cervical cerclage, progesterone, antibiotics prophylaxis, smoking cessation and vitamin D supplementation;[19] however, their overall efficacy is mixed. Recent initiatives such as specialised preterm birth clinics for high-risk women[20] and predictive tools like the QUiPP app, which combines gestational age, history of sPTB and

TABLE 2 Rate of preterm stillbirths and NND per 1000 births by PSANZ-PDC classification by year[†]

	2010	2011	2012	2013	2014	2015	2016	2017	2018	
	n = 74 524	*n* = 74 135	*n* = 78 410	*n* = 78 360	*n* = 79 154	*n* = 79 312	*n* = 80 913	*n* = 79 792	*n* = 78 925	*P*-value
Preterm stillbirths										
Congenital anomaly	2.43	2.29	2.22	2.12	2.05	2.51	2.10	2.23	2.20	0.47
Infection	0.08	0.11	0.14	0.13	0.21	0.26	0.30	0.09	0.16	0.24
Hypertension	0.20	0.13	0.28	0.19	0.14	0.18	0.15	0.05	0.06	**0.02**
Antepartum haemorrhage (APH)	0.43	0.36	0.45	0.32	0.54	0.24	0.31	0.26	0.43	0.38
Maternal conditions	0.12	0.26	0.17	0.14	0.24	0.08	0.07	0.09	0.01	**0.03**
Specific perinatal conditions	0.44	0.49	0.41	0.57	0.38	0.44	0.69	0.70	0.62	0.06
Hypoxic peripartum death	0.05	0.00	0.00	0.01	0.06	0.04	0.02	0.03	0.04	0.70
Fetal growth restriction (FGR)	0.51	0.58	0.45	0.48	0.49	0.48	0.44	0.54	0.58	0.73
Spontaneous preterm birth (sPTB)	0.72	0.53	0.64	0.73	0.51	0.68	0.62	0.58	0.76	0.79
Unexplained antepartum death	0.94	0.92	0.73	0.97	0.96	0.74	0.58	0.70	0.61	**0.02**
Preterm NND										
Congenital anomaly	0.56	0.76	0.88	0.79	0.71	0.68	0.67	0.59	0.67	0.52
Infection	0.05	0.03	0.03	0.03	0.13	0.13	0.17	0.20	0.03	0.25
Hypertension	0.09	0.05	0.01	0.03	0.03	0.03	0.05	0.01	0.06	0.59
Antepartum haemorrhage (APH)	0.17	0.30	0.22	0.23	0.25	0.24	0.15	0.28	0.14	0.41
Maternal conditions	0.04	0.08	0.00	0.04	0.06	0.01	0.06	0.01	0.03	0.18
Specific perinatal conditions	0.11	0.18	0.15	0.41	0.25	0.18	0.26	0.24	0.25	0.13
Hypoxic peripartum death	0.03	0.03	0.01	0.03	0.08	0.01	0.01	0.03	0.03	0.80
Fetal growth restriction (FGR)	0.01	0.08	0.06	0.01	0.04	0.00	0.02	0.03	0.03	0.72
Spontaneous preterm birth (sPTB)	1.30	0.85	0.87	0.98	0.81	0.62	0.68	0.74	0.85	0.06
No obstetric antecedent	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.67

[†]Perinatal deaths due to TOP for MPI are excluded.
Bold values represent statistical significance.

fetal fibronectin measurements among women with threatened preterm labour,[21] offer a promising approach; however, they are not routinely used in Australian clinical practice nor are they applicable to primiparous women. Future research in this area is vital to reduce the rate of preterm perinatal death.

Despite observing a significant reduction in the rate of stillbirths that are considered 'unexplained' over the study period, almost 10% of extremely preterm stillbirths and approximately one-fourth of those in later periods were classified as such, remaining the second most common category of stillbirth. Investigations such as placental pathology and autopsy are critical to establishing cause of death[22] and yet only ~one-third of perinatal deaths are currently investigated by autopsy which has remained steady over the past decade.[5] Research has shown that clinician and healthcare workers' hesitancy to discuss autopsy and appropriately counsel bereaved parents continue to contribute to this low rate of investigation;[9] however, bereaved parents who do consent to autopsies most often do not regret consenting to an autopsy.[23] As recommended by the PSANZ core set of investigations,[10] placental examination should be performed as a minimum; however, a recent multicentre study has shown that no cases were examined entirely according to these guidelines.[24] Actions to improve perinatal mortality audits, investigations, reporting and autopsies are highlighted in the recent National Stillbirth Action and Implementation Plan.[25] Since 2017, the PSANZ-PDC now includes three subcategories under the 'unexplained' category for more comprehensive classification and to identify those that were not adequately investigated, which may explain the observed reduction in unexplained antepartum deaths.

FGR is well established as a risk factor for perinatal death regardless of gestation.[26] We found that 9.1% of all preterm stillbirths and 1.4% of NNDs were classified as FGR (not associated with other conditions) which was more prevalent in the later preterm gestations. The detection of FGR, however, remains a challenge, with less than 20% of FGR infants being detected antenatally overall.[26] Even when detected, management of early-onset FGR is challenging due to a lack of interventions, and current approaches require balancing the risks of stillbirth against comorbidities of prematurity.[27] Modifiable risk factors for FGR include smoking and elevated BMI (>30 kg/m^2), and thus improving smoking cessation rates is a key component of the national stillbirth prevention strategy, the Safer Baby Bundle.[28] Future research focusing on FGR interventions to identify, monitor and prevent FGR or allow prolongation of pregnancy is needed. In recent updates to the PSANZ-PDC, FGR has now been replaced with 'placental dysfunction or causative placental pathology' to better reflect this category. One category which did see a reduction, hypertension, may be the result of recent recommendations to take low-dose aspirin in early pregnancy to manage hypertension and prevent preeclampsia[29] or changes in population demographics. Future research is needed to better understand this.

This study had some limitations; firstly it is ecological in nature and as such we have been unable to explore the relationship between potential risk factors for preterm perinatal deaths. Secondly, due to the way the data is summarised in the reports, we are unable to determine the number of congenital anomalies within each gestational group that were TOPs. Finally, while PSANZ coding is explicit and performed by trained clinicians, there are some differences in the way perinatal deaths were classified over time and we did not investigate the PSANZ-PDC subcategories in greater depth. A strength of our study is that we were able to exclude TOPs for MPI, which represented almost a quarter of all preterm perinatal deaths. National stillbirth reports tend not to consider TOP due to differences in jurisdictional data collection. This contribution of TOPs to preterm stillbirth rates may be overestimating Australia's stillbirth rate overall and masking where strategies should be targeted to reduce the rates of stillbirth further.

In conclusion, we found that overall, both preterm stillbirth and preterm NND share common causes; however, there are differences between gestational groups. Strategies to reduce the rates of preterm perinatal deaths in Australia should focus on interventions that aim to reduce the rates of congenital anomaly and sPTB and improve the detection and management of early FGR. Increases in the rates of autopsy and investigations are also desperately needed and will help us to further reduce perinatal deaths that are 'unexplained'. Future research to understand the underlying pathways leading to perinatal death is essential to determine where commonalities lay between stillbirth and NND, and we highlight the importance of including both types of perinatal deaths in such analyses.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix. PSANZ Perinatal Death Classification (PSANZ-PDC).