Does antenatal care timing influence stillbirth risk in the third trimester?: a secondary analysis of perinatal death audit data in South Africa

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Abstract

Objective: To explore stillbirth risk across gestation in three provinces of South Africa with different antenatal care schedules.

Design: Retrospective audit of perinatal death data using South Africa's Perinatal Problem Identification Program.

Setting: In 2008, the Basic Antenatal Care Programme was introduced in Limpopo and Mpumalanga provinces, reducing appointments to five visits at booking, 20,26,32,38 weeks and 41 weeks if required . In the Western Cape province seven appointments remained at booking, 20,26,32,34,36,38 and 41 weeks if required.

Population: All audited stillbirths (n=4211) between October 2013 to August 2015 in Limpopo, Mpumalanga and Western Cape.

Methods:

Stillbirth risk (26-42 weeks gestation,>1000g) across gestation was calculated using Yudkin's method. Stillbirth risk was compared between provinces and relative risks calculated between Limpopo/ Mpumalanga and Western Cape.

Main Outcome measures:

Stillbirth risk across gestation

Results:

Stillbirth risk peaked at 38 weeks gestation in Limpopo (relative risk (RR) 3.11,95%CI2.40-4.03,p<0.001)and Mpumalanga (RR 3.09,95%CI2.37-4.02,p<0.001) compared to Western Cape where no peak was observed. Stillbirth risk at 38 weeks in Limpopo and Mpumalanga were statistically greater than both 37 and 39 weeks stillbirth risk within provinces (p<0.001). As expected a peak at 41 weeks was observed in all provinces.

Conclusions:

The increased period of stillbirth risk occurs after a six week absence of antenatal care. This calls for a refocus on the impact of reduced antenatal care visits during the third trimester.

Tweetable abstract: Reduced antenatal care in the third trimester may increase stillbirth risk

Key words: stillbirth, antenatal care, South Africa, perinatal mortality

Introduction

High on the global health agenda is accelerating progress to end preventable stillbirths.[1, 2] In 2014, the Every Newborn Action Plan set a target of 12 or fewer stillbirths per 1000 in every country by 2030.[3] South Africa is still above this target with a rate of 17.6 per 1000 births.[4] The provision of antenatal care is crucial in reducing stillbirths.[5] It is estimated that 50% of stillbirths have a maternal complication.[6] Resource limitations in many low-and-middle-income countries, where the majority of deaths take place,[3] make the correct timing and frequency of appointments important in preventing avoidable deaths.

In 2001, the World Health Organization (WHO) conducted the Antenatal Care Trial across clinics in four countries with 22000 women. This randomised controlled trial suggested that five focused antenatal care visits were adequate to ensure good birth outcomes for both mother and baby and avoid adverse outcomes such as low birth weight and postpartum anaemia.[7] After the publication of this data many countries reduced their antenatal schedules to four or five visits. The current WHO model for antenatal care for low risk pregnancies, as informed by the WHO Antenatal Care Trial is a schedule of five focused visits: at booking, 20, 26, 32, 38 weeks with an appointment at the hospital at 41 weeks.[7] Recent analyses in the literature are beginning to re-examine the issue of third trimester antenatal care visits in relation to stillbirth.[8, 9] An updated Cochrane review published in 2015 found that in low-and-middle-income countries perinatal mortality was significantly higher in reduced antenatal care visit groups receiving five or fewer visits compared to standard antenatal care visits.[8] A secondary analysis of the WHO Antenatal Care Trial also found an increased relative risk of fetal death of 27% between 32 and 36 weeks gestation in populations with reduced antenatal care schedules.[9]

In South Africa, in 2008 all provinces but one adopted the reduced antenatal care schedule, giving us the unique opportunity to evaluate the impact of reduced antenatal care visits in the third trimester on stillbirth risk across gestation by comparing perinatal mortality data from three selected

provinces: Limpopo, Mpumalanga , Western Cape. In Limpopo and Mpumalanga antenatal care visits occurred at booking and 20,26,32,38 weeks (+41 weeks if required), while in Western Cape visits occurred at booking, 20,26,32,34,36,38 weeks (+41 weeks if required).

Methods

Evaluation of stillbirth risk and antenatal care timing

Secondary analysis of the South African Perinatal Problems Identification Program (PPIP) database allowed for the analysis stillbirth risk across gestation, which could be compared between the three provinces between October 2013 and August 2015 inclusive. PPIP is a perinatal quality audit system that has been described in detail elsewhere.[6, 10] Briefly, at each clinical site across the three provinces the clinical team perform a death review shortly after a death has occurred. The primary obstetric cause of death was defined by the PPIP technical team as the main obstetric event or pregnancy occurrence which was integral in the pathway to perinatal death, as described in other published work.[11] Macerated stillbirth was clinically diagnosed as a baby where the skin was discoloured, blotchy and friable to touch; a fresh stillbirth was clinically diagnosed as a baby with the skin intact and 'normal' in appearance. These dates and provinces were chosen as they introduced the PPIP V3 in the middle of 2013; this new version included the gestational age and the maternal condition at birth for all perinatal deaths for the first time. In all three provinces over 90% of perinatal deaths were audited by PPIP. Gestational age was calculated based on date of last menstrual period, ultrasound or clinical examination and cases were excluded if the gestation age was unknown or if the estimated age was considered 'uncertain'. No hierarchy was employed in determining gestational age. Using PPIP we extracted detailed data on all stillbirths weighing >1000g and >26 weeks gestation. Only women who had reported receiving antenatal care were included.

The PPIP program has ethical approval from the University of Pretoria. The data is collected with permission from the South African Department of Health. This secondary analysis was approved by the PPIP technical task team and UWA Human Ethics Committee.

Statistical Analysis

Stillbirth rate

Stillbirth rate was calculated using the number of stillbirths/the number of births and expressed as stillbirths per 1000 live births. Overall incidence of stillbirth for the study period was conducted as well as cumulative stillbirth rate at each gestational age.

Stillbirth risk

A fetuses-at-risk (FAR) approach was adopted using Yudkin's (1987) method of stillbirth risk calculation. This approach considers the number of fetuses still in-utero as the population at risk .[(12)] As there were no live birth data available for Limpopo, Mpumalanga or Western Cape with information on gestational age an alternative approach had to be used. Therefore data on live births with information on gestational age was used from Mamelodi subdistrict. Several steps were undertaken: 1) The proportion of live births in each birth weight category (500-999g; 1000-1499g;1500-1999g;2000-2499g, 2500+g) for Mpumalanga, Limpopo and Western Cape were compared with the proportion of live births in each birth weight category for Mamelodi. There were no significant differences in the proportion of live births occurring in each birth weight category between the provinces and Mamelodi so we were able to assume that the distribution across gestation would also be similar.; 2) The distribution of live births across gestation from Mamelodi was plotted i.e. the proportion of all live births for Mamelodi that occurred at each gestational age (e.g. at 26 weeks 0.49% of infants were born, at 38 weeks 17.67 % of infants were born); 3) The proportion of live births at each gestational age in Mamelodi was applied to the number of known births in Mpumalanga, Limpopo and Western Cape (e.g. at 26 weeks 0.49% of infants were born, at

38 weeks 17.67 % of infants were born); 4). Sensitivity analysis was conducted by as outline below. At each gestational age stillbirth risk was calculated using the number of stillbirths divided by the total number of unborn fetuses for each province (separately) as expressed as the number of stillbirths per 1000 fetuses still in utero.

Relative Risk

Relative risk was calculated between Limpopo/ Mpumalanga and Western Cape at each gestation age critical such as 32, 38 and 41 weeks. Relative risk was also calculated within provinces between large increases/decreases, for example between 37-38 weeks and 38-39 weeks. A P-value of <0.01 was considered statistically significant.

Hazard ratio

A proportional hazard approach was adopted to compare stillbirth risk across gestation between Limpopo/Mpumalanga with Western Cape. The Cox regression model used an interaction term for province*time across gestation (grouped as a factor) across the gestational period. The time periods adopted were <33 weeks, 34-36 weeks, 37 weeks, 38 weeks, 39 weeks, 40+ weeks. Hazard Ratios and 95% Confidence Intervals were calculated at each time point for the comparisons between provinces.

Primary Cause of Death

Pearson's chi-squared was used to test statistical differences in the proportion of deaths for primary cause of death between provinces, for example hypertensive disorders. The difference in the proportion of stillbirths by mothers condition (mother complication Y/N) was also tested using Pearson's chi-squared.

Sensitivity Analysis

As live birth data was derived from Mamelodi subdistrict rather than Limpopo, Mpumalanga or Western Cape we conducted a sensitivity analysis to ensure that the use of live birth data from Mamelodi was a reasonable and valid approach. A series of hypothetical changes to the distribution of live births across gestational age were implemented and the impact on the risk estimates assessed.

Results

There were 528727 births over 1000g in the study period between October 2013-August 2015 (Limpopo =209768; Mpumalanga =145362; Western Cape= 173597), of these births 8111 were stillbirths (Limpopo=3808; Mpumalanga =2501; Western Cape=1802). After exclusion of stillbirths prior to 26 weeks, stillbirths with unknown or uncertain gestation and women who had not received antenatal care, the number of stillbirths used for analysis was 4211 (Limpopo n=1968; Mpumalanga n=1533; Western Cape n=710). There were no statistically significant differences in the proportion of women between 'certain' gestational age and 'uncertain' gestational age groups in terms of maternal age, parity, HIV status or syphilis status. The only exception was in Western Cape where the 'uncertain' gestational age group was younger than the 'certain' gestational age group (15-24 years uncertain 49.6%, certain 40.5%, p=0.0369).

The cumulative incidence of stillbirth for the study period was highest in Limpopo (18.5 per 1000 live births) and Mpumalanga (17.5/1000) compared to Western Cape (10.5/1000). In terms of the stillbirth rate across gestation, although Western Cape had a lower stillbirth rate consistently across gestation compared to the other two provinces the pattern was the same for all three provinces. The cumulative stillbirth rate increased between 26 to 31 weeks gestation then declined steadily after 31 weeks gestation (Figure 1). At 38 weeks the stillbirth rate for Limpopo was 17.2/1000 live births, Mpumalanga 17.1/1000 and Western Cape 5.44/1000.

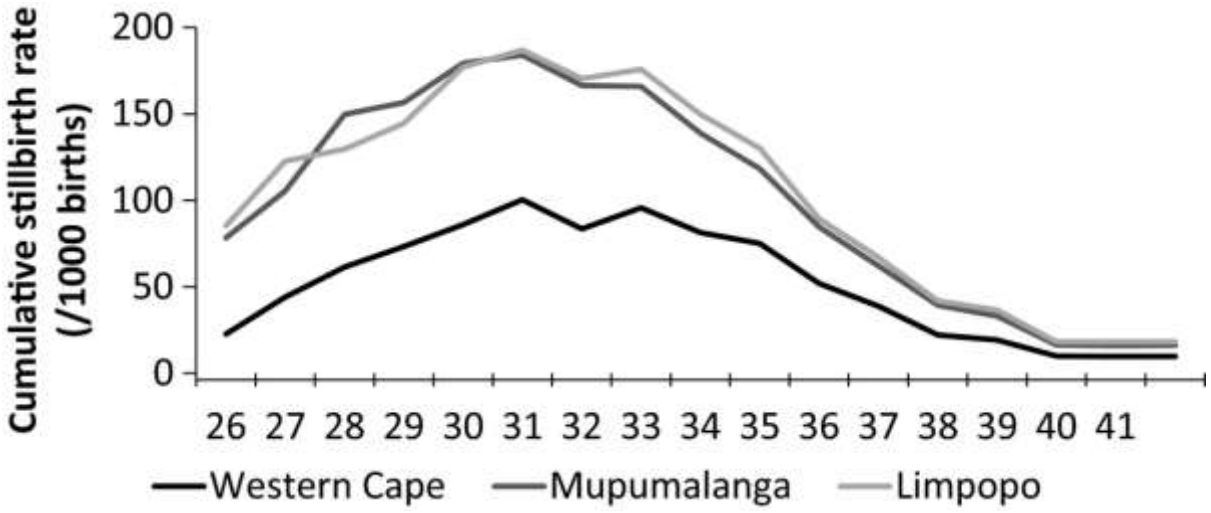

Figure 1. Cumulative stillbirth rate/1000 births (stillbirths and live births) for Western Cape, Mpumalanga and Limpopo across gestational age.

When examining stillbirth risk (number of stillbirths/number fetuses still in-utero), Limpopo and Mpumalanga showed increased stillbirth risk at 38 weeks which was significantly different to both Western Cape 38 week stillbirth risk ($p<0.001$) and also stillbirth risk at 37 and 39 weeks ($p<0.001$) within each province (Figure 2). In Western Cape no peak was observed at 38 weeks. At 38 weeks stillbirth risk was 3.63 per 1000 fetuses still in-utero for Limpopo, , 3.61 per 1000 for Mpumalanga and 1.16 per 1000 for Western Cape. The relative risk of stillbirth at 38 weeks was 3.11(95%CI2.40-4.03;$p<0.001$) for Limpopo and 3.09(95%CI2.37-4.02;$p<0.001$) for Mpumalanga compared to Western Cape. The relative risk for stillbirth at 38 weeks compared to 37 weeks and 39 weeks was 1.76(95%CI1.47-2.09;$p<0.001$) and 1.50(1.24-1.80;$p<0.001$), respectively for Limpopo. In Mpumalanga the RR was 2.15(95%CI1.76-2.63;$p<0.001$) at 38 weeks compared to 37 weeks and 2.41(95%CI1.90-3.05;$p<0.001$) compared to 39 weeks. In all provinces an increase in stillbirth risk was also observed at 41 weeks: Limpopo stillbirth risk 10.2/1000; Mpumalanga 5.6/1000; Western Cape 5.5/1000. The relative risk between Limpopo and Western Cape for stillbirth risk at 41 weeks was 1.8(1.0-3.4;$p=0.048$), while for Mpumalanga the difference was not statistically different (RR1.0;95%CI0.5-2.1;$p=0.920$).

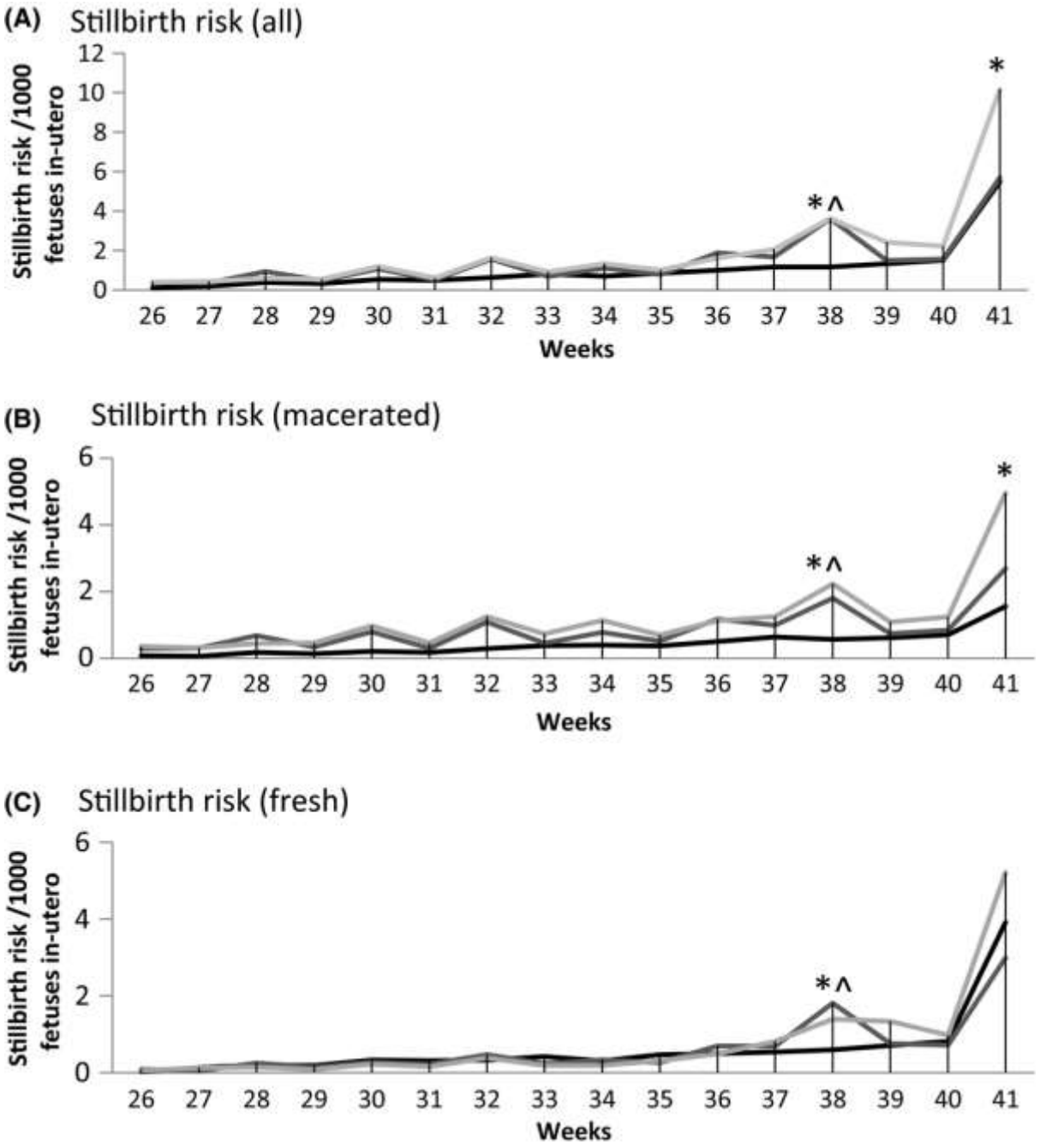

Figure 2. Comparison of stillbirth risk by weekly gestation between provinces and primary cause of stillbirth. A – stillbirth risk (all); B – stillbirth risk macerated; C – stillbirth risk (fresh); * $p<0.05$ with Western Cape 38w; ^$p<0.05$ with 37 and 39 week within province data.

The proportional hazards models showed similar results to the approach using Yudkin's methods of stillbirth risk calculation (Figure 3). There was an increased Hazard Ratio at 38 weeks for both Limpopo (HR 3.1;95%CI2.4-4.1) and Mpumalanga (HR3.1;95%CI2.4-4.0).

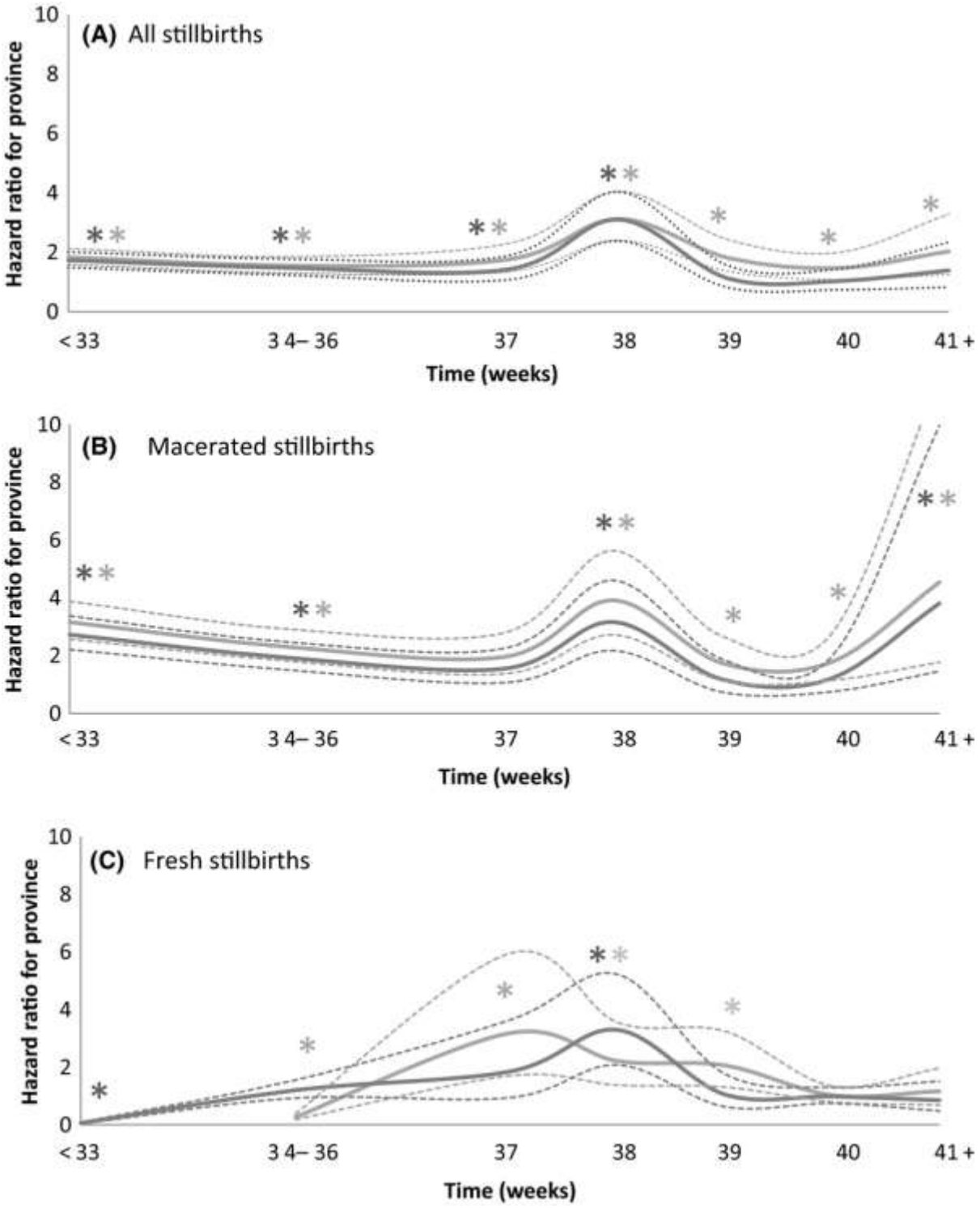

Figure 3. Estimated hazard ratio for stillbirth (dark gray solid line - Mpumalanga; light gray solid line - Limpopo) and 95% confidence intervals (dotted lines) for provinces (relative to Western Cape) as a function of time (<33 w, 34-36w, 37 w, 38w, 39w, 40w, 41w) A. all stillbirths B. macerated stillbirths C. fresh stillbirths. *p<0.05 with Western Cape

Limpopo and Mpumalanga both had statistically greater proportions of deaths due to hypertension than Western Cape ($p<0.001$). Stillbirth from hypertension peaked at 32 weeks(12% of hypertensive deaths) and 38 weeks(11% of hypertensive deaths) in Limpopo and Mpumalanga but in Western Cape there were several peaks across gestation (at 33, 35, 36 weeks). The difference in the proportion of hypertensive related deaths occurring at 32 weeks was significantly higher for Mpumalanga ($p<0.001$) and Limpopo ($p<0.001$) compared to Western Cape. The difference seen at 38 weeks was not statistically significant between provinces but neared significance for the Limpopo ($p=0.064$) compared to Western Cape comparison. Maternal complication occurred in 37.9% of stillbirths in Limpopo; 50% in Mpumalanga, and 45% in Western Cape. The lower proportion of stillbirths with a maternal condition in Limpopo was statistically significant compared to both Western Cape ($p<0.001$) and Mpumalanga ($p<0.001$). Maternal hypertension was present in 23.9% of stillbirths (Limpopo 21.8%; Mpumalanga 28.8%; Western Cape 18.9%).

Sensitivity Analysis

There were no significant differences between the proportion of live births by weight categories (1000-1499g, 1500-1999g, 2000-2499g and 2500+g) between Mamelodi and the three provinces. The largest difference in the proportion of live births occurring in a single weight category was 2.4% between Western Cape and the Mamelodi subdistrict for the 2500g+ category. Therefore a sensitivity analysis was performed by increasing the proportion of live births at each gestational age one at a time by 5% and 20% in individual analyses. Decreasing the proportion of live births by 5% and 20% was also performed in the same manner. There were no significant differences between stillbirth risk prior to adjustment and after adjustment at any gestational age with the increases/decreases implemented. The greatest change in stillbirth risk at 38 weeks was <1%, when a 20% change in the number of live born neonates was implemented at 38 weeks (e.g. in Mpumalanga stillbirth risk changed from 3.61/1000 fetuses in-utero to 3.58/1000). With a 20% increase in the proportion of live births occurring at 38 weeks in Limpopo (Western Cape remained unchanged) the relative risk between Limpopo and Western Cape was 3.09(95%CI2.38-4.00;

p<0.001) compared to 3.11(95%CI2.40-4.03;p<0.001) in the original analysis. For Mpumalanga the relative risk was 3.07(95%CI2.36-3.99; p<0.001) compared to 3.09(95%CI2.37-4.02;p<0.001) in the original analysis. Therefore it was concluded that if even if there was a difference in the distribution of live births at any gestational age at eight times the variation observed in our data it would be unlikely for any substantial changes to occur to our risk estimates.

Discussion

Main findings

This secondary analysis of more than 4000 stillbirths found an unexpected peak in stillbirth risk at 38 weeks in the two provinces with reduced antenatal care schedules. This coincides with the first antenatal care visit after a six week absence of antenatal care. The risk of stillbirth at 38 weeks in both Limpopo and Mpumalanga was around three times that of Western Cape. In all provinces a peak was observed at 41 weeks as expected.[12] In addition a larger proportion of deaths were due to hypertension in both Limpopo and Mpumalanga with a peak in deaths at 32 weeks compared to Western Cape.

Strengths and Limitations

This study used data from a real-world setting that retrospectively evaluated the timing of stillbirths across gestation in relation to antenatal care schedule. Each death was evaluated rigorously by a clinical team. The results from this ecological study must be interpreted with caution. Firstly, these results are for unadjusted statistical models where known confounders such as socioeconomic status and rural location have not been controlled for. These data were aggregate clinical data, which did not contain information on SES or proxy indicators for SES. This limited our ability to adjust for confounding in our models and apply sensitivity analyses such as the principle-stratification approach as published in other studies. [13, 14] While it is recognised that Western Cape is a wealthier province which would likely influence stillbirth rate (as shown in Figure 1), SES should not affect the patterns observed in stillbirth risk across gestation i.e. there is no specific gestation at which one

would expect stillbirth risk to be increased in a higher SES population compared to a lower SES population. Not adjusting for SES across provinces would also not influence stillbirth risk across gestation in each province i.e. the increased stillbirth risk specifically at 38 weeks.

Secondly, the study was limited by not having live birth data with gestational age for Limpopo, Mpumalanga and Western Cape, therefore data from Mamelodi subdistrict was used to inform our analysis around stillbirth risk. However, the sensitivity analysis revealed that even large, unrealistic changes to the proportion of live births at any gestational age would not be likely confer a large change to our estimates.

Interpretation

We used Yudkin's method which is a fetuses-at-risk (FAR) approach to calculate stillbirth risk. In our data examining stillbirth risk using the FAR approach revealed a critical period at 38 weeks gestation, which would not have been revealed if using stillbirth rate as a measure of risk. An extension on Yudkin's method of stillbirth risk calculation is to use a modified Cox regression model designed for perinatal mortality studies adopting the FAR approach, where time-dependant effects such as gestational age must be considered.[15] This model has been used in numerous studies that examine fetal death using the FAR approach. [16, 17] Due to the nature of our data, issues with convergence prevented us from using this method. This method had it worked would arguably have been a more appropriate method to use.

Interestingly our analysis found similar findings to the Cochrane review and WHO Antenatal Care Trial secondary analysis when observing the peak at 38 weeks gestation. Our main observation was an unexpected peak in stillbirth risk at 38 weeks in the two provinces that had reduced antenatal care schedules. The peak in stillbirth risk observed at 38 weeks in the provinces with reduced antenatal care schedules is consistent with the secondary analysis of the WHO Antenatal Care Trial. The trial revealed an increased relative risk of 24% for fetal death between 32 and 36 weeks gestation in countries with reduced antenatal care schedules in both low and high risk groups. [9] In both studies the risk of death increased specifically during the period when no antenatal care was

delivered. The recent Cochrane review found that in low-and-middle-income countries perinatal mortality was significantly higher in the reduced antenatal care visit groups, with an increased risk ratio of 15%.[8] This was largely attributed to the WHO Antenatal Care Trial were an increase in stillbirths amongst the reduced visit group was observed.[8]

The reason for the observed peak at 38 weeks in the provinces with reduced antenatal care but not Western Cape where antenatal care continues fortnightly is unclear. Western Cape has better maternal and perinatal outcomes, as reflected by the lower stillbirth rate observed in the province which may account in part for the absence of a peak in stillbirth risk at 38 weeks. It is also notable that the peak in stillbirth risk at 41 weeks occurs as with the other two provinces. Although a lack of antenatal care during this time is a plausible explanation for the higher stillbirth risk seen in Limpopo and Mpumalanga at 38 weeks [9] it is unclear if the absence of a peak in stillbirth risk at 38 weeks in Western Cape is due to more frequent antenatal care in the third trimester or due to better quality antenatal care or another unknown reason. The combination of frequent antenatal care as well as better quality antenatal care is likely to contribute as any fetuses at risk of stillbirth may be identified at antenatal care appointments but also managed clinically. It is also important to remember that the peak at 38 weeks is likely to reflect diagnosis of stillbirth rather than time of fetal demise, however it is interesting that the diagnosis of stillbirth for both fresh and macerated stillbirths was increased at 38 weeks. This indicates that deaths occurred during the period between 35-38 weeks (macerated stillbirth) [18] or closer to 38 weeks (fresh stillbirths), both during a period when no antenatal care visits were scheduled. Recently a critical period for small-for-gestational age babies has been observed between 33-37 weeks gestation, with the largest proportion of stillbirths occurring during this period.[11] This critical period falls during a time when no antenatal care is delivered in Limpopo or Mpumalanga. Other studies exploring the timing of antenatal care and stillbirth risk have also concluded that lack of antenatal care is a plausible explanation. [8, 9] The WHO Antenatal Care Trial secondary analysis concluded that the peak in deaths during this period may be due to the reduced number of visits,[9] while the Cochrane review concluded that having only two or

three visits scheduled in the third trimester would not be sufficient to detect fetuses at risk or provide treatment to prevent stillbirth, thus contributing the increased risk of perinatal death in the reduced antenatal care group.[8] It is unknown if visits during this time at 34 weeks and 36 weeks gestation (as in Western Cape) would precede the peak in stillbirth diagnosis at 38 weeks and allow time for intervention. The average time between the last antenatal care visit and a maternal near miss event due to hypertension is 2.6weeks[19] this is around the same time frame for fetal demise in macerated stillbirths. Perhaps additional antenatal care appointments scheduled should consider this lead time to identify maternal complications and potentially decrease stillbirth risk.

Conclusion

It is difficult to determine from the current study's findings if stillbirth risk increases when antenatal care appointments are reduced in the third trimester, however it appears to be a plausible explanation for the increase in stillbirth risk seen in the current study. Perhaps there is a need to re-focus attention on third trimester antenatal care visits and the impact on stillbirth given the recent advances in the literature. Further research is needed in this area given the large number of stillbirths occurring in the third trimester globally every year. [3]

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Contribution to authorship: TL contributed to conceptualisation of study, analysed data, drafted manuscript; RP conceptualised study, analysed data, revised and edited manuscript.

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Department of Health. This secondary analysis was approved by the technical task team of the South African Medical Research Council. Ethics approval was given from the UWA Human Ethics Committee (RA/4/1/7955, 20/11/2015).

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