Pregnancy-Related Deaths Due to Pulmonary Embolism: Findings from Two State-Based Mortality Reviews

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Abstract This report presents findings from two state-based pregnancy-related reviews of deaths due to pulmonary embolism to describe prevalence, risk factors, and timing of symptoms and fatal events (N = 46). We examined the utility of state-based maternal mortality review teams as a means to gain more complete data on maternal deaths from which guidelines for prevention and intervention can be developed. The Florida Pregnancy-Associated Mortality Review Team and Virginia Maternal Mortality Review Team collaborated on findings from 9 years of pregnancy-related mortality review conducted in each state. Pregnancy-related deaths due to pulmonary embolism occurring within 42 days of pregnancy between 1999 and 2007 in Florida and Virginia were identified. Retrospective review of records was conducted to obtain data on timing of the fatal event in relation to the pregnancy, risk factors, and the presence and timing of symptoms suggestive of pulmonary embolism. Forty-six cases of pregnancy-related death due to pulmonary embolism were identified. The combined pregnancy-related mortality ratio (PRMR) was 1.6/100,000 live births. The PRMR for patients undergoing cesarean section delivery was 2.8 compared to 0.2 among those with vaginal deliveries (95 % CI = 1.8–4.2 and 0.1–0.5 respectively). Women aged 35 and older had the highest PRMR at 2.6/100,000 live births. BMI over 30 kg/m^2 and presence of chronic conditions were frequently identified risk factors. One in five decedents (21.7 %) reported at least two symptoms suggestive of pulmonary embolism in the days before death. This combined state-based maternal death review confirms age over 35 years, obesity, and the presence of chronic conditions are risk factors for pregnancy-related mortality due to venous thromboembolism in the US. Expanding and standardizing the process of state-based reviews offers the potential for reducing pregnancy-related mortality in the US.

Keywords Pregnancy-related mortality ·
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Efforts to decrease pregnancy-related mortality in the United States begin with a thorough understanding of the factors and circumstances leading to each death. A 2010 report on pregnancy-related mortality in the United States from 1998 through 2005 was published using the Pregnancy Mortality Surveillance System data [1]. The authors conclude that state-based maternal mortality reviews could potentially lead to improved understanding of the context in which women suffer these deaths. Although there is now improvement in understanding the clinical cause of death through the national Pregnancy Mortality Surveillance System, a deeper level of information about each death can only be achieved by state review committees.

Venous thromboembolism (VTE) now accounts for approximately 10 % of all pregnancy-related deaths in the United States [1]. Berg et al. [1] reported 478 pregnancy-related deaths due to thrombotic pulmonary embolism between 1999 and 2005. Based on total live births for the time period [2], the maternal mortality ratio for VTE is 1.5 deaths per 100,000 live births. Clark et al. [3] concluded that the most feasible means of reducing the American pregnancy-related mortality ratio is through nationwide systematic prevention efforts targeting death due to pulmonary embolism. Citing this report, the Joint Commission issued a Sentinel Event Alert on the prevention of maternal death. They recommended the use of pneumatic compression devices for patients undergoing cesarean section delivery and evaluation of patients at high risk for VTE for low molecular weight heparin (LMWH) postpartum [4]. The Joint Commission identified preexisting conditions such as hypertension, diabetes, and morbid obesity as high risk conditions. Additionally, the American College of Obstetricians and Gynecologists (ACOG) recently published clinical management guidelines on thromboembolism in pregnancy [5]. These guidelines target women with a history of VTE or with acquired or inherited thrombophilias as well as all women undergoing cesarean delivery.

The government of the United Kingdom mandates that a specific committee perform in-depth reviews of all maternal deaths [6]. For more than 50 years, these investigations have garnered acceptance by maternal healthcare workers in a system that separates the legal system's responsibilities for assigning liability and assessing damages from the medical profession's responsibility to improve medical care. Based on their findings, guidelines were written that led to a reduction in maternal deaths in Great Britain. Their recent report showed significant decreases in deaths from thrombosis and embolism in the United Kingdom since the country-wide Maternal Death Enquiry began in 1985 [7]. This decrease followed the 1995 publication of the Royal College of Obstetricians and Gynecologists' (RCOG) guideline for thromboprophylaxis after cesarean section delivery. Further enquiry in the UK revealed the need for practitioners to recognize and respond with adequate prophylaxis antenatally and following vaginal deliveries by high risk women. In 2004, RCOG developed additional guidelines for prophylaxis during pregnancy, labor and after normal vaginal delivery which led to major reductions in antenatal deaths and deaths following vaginal delivery between 2006 through 2008. These two guidelines which cover thromboprophylaxis during pregnancy and labor and after vaginal and cesarean section delivery, led to significant reductions in maternal death. The maternal mortality ratio for death due to pulmonary embolism in the UK in 2006–2008 was 0.79 deaths per 100,000 live births, a decrease from 1.94 for the period from 2003 to 2005 [7].

Examination of these deaths showed that further reductions may still be possible through greater adherence to the guidelines.

In 2010, the Florida Pregnancy-Associated Mortality Review team (PAMR) and the Virginia

Maternal Mortality Review Team (MMRT) began to collaborate on findings obtained from 9 years of pregnancy-related mortality review conducted in each state. These two states are among the longest continually operating multidisciplinary review teams in the United States. This report summarizes findings from these two state-based pregnancy-related reviews of deaths due to pulmonary embolism from VTE, a cause of death that may be reduced through medical interventions. The purpose of this study was to use state-based reviews to describe current VTE deaths and to examine potential opportunities to further reduce them in our two states.

Materials and Methods

Mortality review provides a theory and method for identifying and understanding risk factors within a population. Grounded in public health and focused on prevention, these reviews involve in-depth examination of the circumstances surrounding death. Mortality reviews function to improve understanding of all factors influencing the problem so that recommendations and interventions can be developed to reduce death. The method of mortality review involves collecting and examining records generated through the investigation of a fatal illness or injury, and in this case, pregnancy-related death.

Both committees in Virginia and Florida follow the Centers for Disease Control and Prevention's (CDC) recommendations set forth in Strategies to Reduce Pregnancy Related Deaths [8]. Vital Records Offices in both states identify cases of pregnancy-associated death (deaths occurring in a woman who was pregnant at the time of death or had a pregnancy in the year prior to death) in three categories: (1) examining the death certificate check box related to pregnancy status; (2) reviewing death certificate cause of death indicating death was directly attributable to pregnancy; and (3) matching death certificates of women of reproductive age with birth and fetal death certificates to identify deaths occurring among women who delivered in the year preceding death. Florida also links death certificates to a state mandated prenatal risk screen of all pregnant women through Florida Healthy Start. The overall percentage of women screened ranged from 81 to 86 % in 2009 and 2011 respectively.

Using information obtained from the death certificates, birth certificates, and fetal death certificates, the review teams find and review records or abstracts of records from

the hospital where the birth or pregnancy termination occurred, the birth attendant's records, hospital records where the death occurred, the autopsy records, and the Medical Examiner case investigation records.

From mortality review data in Virginia, cases for this report were included if the cause of death as listed on the official maternal Death Certificate included "pulmonary embolism" as the cause of death or as a related factor, or if pulmonary embolism was found at autopsy whether or not the cause of death included pulmonary embolism. In Florida reviewers also included the case if the team review concluded that pulmonary embolism was the underlying cause of death. For both states, a postpartum death for this study must have occurred within 6 weeks (42 days) of the end of the pregnancy.

After identifying all relevant cases, we reviewed available records to determine age, race, parity, height, and pre-pregnant weight from which the decedent's body mass index (BMI) was calculated, presence of a chronic condition, presence or history of gestational hypertension or preeclampsia, preterm labor, history of infection or anemia, utero-placental problems, previous fetal loss or stillbirth, personal or family history of thromboembolism, route of delivery, and timing of death in relation to the pregnancy and delivery. We also noted if symptoms suggestive of pulmonary embolism (shortness of breath, pain or weakness in the legs, tachycardia, or chest pain) were reported at least 1 day prior to death. Pregnancy-related mortality ratios are calculated using birth certificate data and the standard definition of deaths/100,000 live births.

The projects have received exemption from their respective Institutional Review Boards because all subjects are deceased, case summaries contain no identifying information, and results are published only in aggregate.

Results

We found a total of 46 pregnancy-related deaths attributed to pulmonary embolism in Virginia and Florida between January 1999 and December 2007. Type of delivery was known in all but one case. In 37 of the 46 cases, medical examiner death investigation records or autopsies were reviewed. In the remaining nine cases without postmortem investigation, hospital death records were reviewed.

The following records were available for review: prenatal (n = 34; 73.9 % of all cases) and delivery (n = 30; 85.7 % of cases in which there was a delivery). Eleven cases (23.9 % of all cases) had neither prenatal nor delivery records. In seven of these 11 cases, death occurred during the pregnancy, at 7–23 weeks estimated gestational age. In the remaining four cases, death occurred 12–31 days after discharge following delivery. Available death records included hospital (n = 32; 69.6 % of all cases), medical examiner death

investigation records (n = 27; 58.7 % of all cases), and autopsy reports (n = 33; 71.7 % of all cases).

Mean parity for the 46 women who died was 2.47 (SD 1.375; range 0–7). Together the 46 decedents left 99 living children.

Pregnancy-Related Mortality Ratio for Thromboembolic Deaths

The combined pregnancy-related mortality ratio for these thromboembolic deaths for Florida (n = 31; 1,945,166 total live births for the time period) and Virginia (n = 15; 915,607 total live births for the time period) is 1.6 per 100,000 live births which is similar to the national rate of 1.5. Comparison of ratios across two time periods was conducted to examine stability over time. Divided roughly at the midpoint, ratios from the two time periods (1999–2003 and 2004–2007) showed no significant change over time ($p = 0.58$). For the latter period, there were 23 deaths and 1,343,759 live births for a mortality ratio of 1.7/100,000 live births. In the earlier period, there were a total of 22 deaths with 1,517,014 births giving a pregnancy-related mortality ratio of 1.4.

The thromboembolic-specific pregnancy-related mortality ratio for African American women was 4.5 times higher than for Caucasian women: 4.1 and 0.9 respectively. Overall, for African American and Caucasian women combined, the mortality ratio was highest for women aged 35 years and older: ≤19 years, PRMR = 0.6; 20–24 years, PRMR = 1.5; 25–34 years, PRMR = 1.5; ≥35 years, PRMR = 2.6. Table 1 shows pregnancy-related mortality ratios and 95 % confidence intervals by age, race, and type of delivery.

Timing of Death and Type of Delivery

Sixteen (35.5 % of patients with known delivery type, n = 45) of all thromboembolic deaths were deemed to have their genesis antenatally; 11 deaths were antenatal deaths and five deaths took place when antenatal maternal distress or demise was then followed by cesarean delivery. These deaths occurred between four and 40 weeks of gestation. Eight [8] deaths occurred in the first trimester (one at 4 weeks, two at 7 weeks, two at 8 weeks, two at 11 weeks, and one at 12 weeks of gestation); two [2] occurred in the second trimester (at 16 weeks and 23 weeks); and six [6] in the third trimester (27, 28, 30, 32, 36, and 40 weeks of gestation).

Twenty-nine deaths occurred after delivery. All of the deaths following vaginal delivery occurred after hospital discharge, at 6, 17, 20, 23, and 39 days post-delivery. Eleven of the 24 deaths following cesarean section delivery occurred within 11 days of delivery and before discharge. The remaining 13 deaths occurred between 4 and 36 days postpartum and after discharge.

Table 1 Pregnancy-related mortality ratio and 95 % confidence intervals by age, race, type of delivery, 1999–2007 (N = 46)

	No. of deaths	PRMR
Age		
<20 years old	2	0.6 (0.1–2.2)
20–24 years old	11	1.5 (0.7–2.7)
25–34 years old	22	1.5 (0.9–2.3)
35 years old and above	11	2.6 (1.3–4.6)
Race		
African-American	26	4.1 (2.7–6.0)
Caucasian	18	0.9 (0.5–1.4)
Other	2	1.2 (0.1–4.3)
Type of delivery[a]		
C-section	24	2.8 (1.8–4.2)
Vaginal	5	0.2 (0.1–0.5)

[a] Excludes antenatal deaths and one death with unknown delivery type

Risk Factors by Timing of Death

Table 2 displays the number and percent of women experiencing each identified risk factor by type of delivery.

The most frequently reported risk factor among women with antenatal VTE was presence of a chronic condition (62.5 %). A majority (56.4 %) of women who died from antenatal thromboembolism were categorized as obese by BMI status. The next most frequent risk factor involved was a history of preterm labor or abdominal pain (43.8 %). All of the seven antenatal women reporting abdominal pain did so within 5 days of death. Finally, 37.5 % reported a history of infections that included upper respiratory infections and/or sexually transmitted infections such as Chlamydia, gonorrhea, or bacterial vaginosis. More than half (56.3 %) had four or more risk factors identified.

The most frequently reported risk factor for women who died from pulmonary embolism after a cesarean delivery

Table 2 Presence of risk factors by type of delivery (N = 45)

	Antenatal (n = 16)		Cesarean section delivery (n = 24)		Vaginal delivery (n = 5)	
	Number	%	Number	%	Number	%
BMI category (kg/m^2)						
Underweight (<20.0)	0	0.0	1	4.2	1	20.0
Normal (20.0–24.9)	5	31.3	1	4.2	0	0.0
Overweight (25.0–29.9)	2	12.5	6	25.0	2	40.0
Obese class I (30.0–34.9)	7	43.8	7	29.2	0	0.0
Obese class II (35.0–39.9)	1	6.3	4	16.7	0	0.0
Obese class III (40.0 and above)	1	6.3	5	20.8	2	40.0
Parity ≥4	3	18.8	4	16.7	2	40.0
Presence of chronic condition (yes)	10	62.5	15	62.5	3	60.0
Family history of embolism (yes)	0	0.0	3	12.5	0	0.0
Personal history of embolism (yes)	3	18.8	2	8.3	0	0.0
Previous pregnancy loss (yes)	3	18.8	8	33.3	2	40.0
Prior stillbirth (yes)	1	6.3	1	4.2	2	40.0
History of pregnancy induced hypertension/eclampsia (yes)	2	12.5	10	41.7	2	40.0
History of preterm labor/abdominal pain (yes)	7	43.8	11	45.8	1	20.0
Utero-placental problems (yes)	5	31.3	16	66.7	1	20.0
History of anemia (yes)	5	31.3	6	25.0	1	20.0
History of infections (yes)	6	37.5	9	37.5	3	60.0
Number of risk factors per case						
0	0	0.0	0	0.0	0	0.0
1	1	6.3	2	8.3	0	0.0
2	3	18.8	2	8.3	2	40.0
3	3	18.8	5	20.8	1	20.0
4	8	50.0	2	8.3	0	0.0
5+	1	6.3	13	54.2	2	40.0

was uterine and placental problems (66.7 %). These included the presence of adhesions, fibroids, placenta accreta, abruption, and/or infarction. The second most reported risk factor was obesity (66.6 %) followed by the presence of a chronic condition (62.5 %), and a history of preterm labor or abdominal pain in 45.8 % of cases. The majority of women (62.5 %) had at least four risk factors identified from their records.

Since only five women died following vaginal delivery, no clear pattern was observed regarding BMI category, or other risk factors. Three of the five women reported chronic conditions, two with hypertension and one with heart palpitations. Three women also reported urinary tract infections. Notably, two [2] women had five [5] risk factors present. These women died at six [6] and 20 days postpartum.

Attempts to Prevent Embolism

Three women were receiving prophylactic anticoagulation when they died. All three had a previous history of VTE. One death occurred antenatally at 7 weeks EGA and two were placed on prophylaxis following cesarean section delivery. An additional decedent had completed warfarin therapy for VTE more than 6 months prior to the pregnancy but was not on prophylaxis at the time of death. Sequential compression devices were utilized in one case following cesarean section delivery due to left leg varicosities.

Neither evidence of anticoagulation treatment nor evaluation of coagulation status was found among those who died following vaginal delivery. There was also no evidence of an increase in anticoagulation therapy or evaluation for coagulopathy over time comparing the time periods before and after 2004.

Presence of Symptoms of Pulmonary Embolism

Signs and symptoms of possible pulmonary embolism reported at least 1 day prior to maternal demise could be determined from the records. They included shortness of breath reported by 34.7 % (n = 16), tachycardia (30.4 %, n = 14), leg pain or weakness (19.6 %, n = 9), and chest pain (13.0 %, n = 6). Ten decedents (21.7 %) reported at least two symptoms during the days before death.

Discussion

This report confirms that pregnancy-related death from pulmonary embolism remains at measurable and constant levels in Florida and Virginia. The pregnancy-related mortality ratio attributable to pulmonary embolism is 1.6

per 100,000 live births over this 9-year period which is nearly identical to that calculated from a national surveillance study. Information collected as part of state-based maternal mortality reviews provides a more complete picture of the circumstances surrounding these deaths than can be obtained through surveillance alone. We were able to determine that the majority of women had multiple risk factors for venous thromboembolism, and many had symptoms during the day before death.

Some of these deaths may have been prevented with more timely identification of risk factors and prevention through the use of prophylaxis. This possibility is supported by the reduction in maternal death due to pulmonary embolism achieved in the United Kingdom (UK) after publication of guidelines for thromboprophylaxis in pregnancy [7]. Using criteria established by the Royal College of Obstetricians and Gynecologists entitled, Reducing the Risk of Thrombosis and Embolism During Pregnancy and the Puerperium, published in November, 2009, we were able to identify 14 women who died in Virginia and Florida with risk factors that would have led to classification as intermediate risk for thromboembolism and for whom prophylactic LMWH is recommended for at least 7 days [9].

Clark et al. [3] noted that women undergoing cesarean delivery rarely receive VTE prophylaxis as is routinely given in similar surgical settings. A recent survey of maternal fetal medicine specialists reveals that a paucity of physicians use routine thromboprophylaxis either following cesarean section delivery or following prolonged antepartum bedrest. Thromboprophylaxis here refers to either mechanical (intermittent pneumatic compression devices) or medicinal (anticoagulant drugs) means. Respondents did say that they would use prophylaxis for high risk patients but there was no clear consensus on what constituted risk factors that would warrant that prophylaxis [10].

The complicated web of factors that precedes fatal pulmonary embolism in pregnant and postpartum women requires persistent coordinated effort of health care providers in order to prevent it. Implementation of the American Congress of Obstetricians and Gynecologists' guidelines on clinical management of thromboembolism in pregnancy should markedly reduce these events. We now know from many studies, and from the experience in the United Kingdom, that maternal death due to embolism can be reduced. Two factors, namely age over 35 years and a BMI greater than 30 kg/m^2, are important independent risk factors for venous thromboembolism (VTE) in pregnancy and postpartum as noted in many previous studies [11–13]. African American women are at higher risk than Caucasian women. In this report we also confirm these statements. When these factors are present in combination with other

risk factors, such as the presence of a chronic medical condition, uterine and placental problems or preterm labor, the risk for an event leading to maternal death increases greatly, so that a high level of suspicion for VTE should exist. If these factors are present in addition to symptoms such as shortness of breath, leg pain or weakness and tachycardia, healthcare providers should consider performing evaluation for venous thromboembolism. Increasing provider awareness of associated risk factors and presenting symptoms should foster improved patient education, screening, and treatment protocols leading to a decrease in maternal morbidity and mortality.

This report remains subject to the possibility of incomplete case identification despite great effort expended in both Florida and Virginia to identify all cases of pregnancy-related death through many different processes. Thus, information provided to maternal mortality review committees always limits investigation. Records of the events preceding and at the time of a death often are incomplete or may be withheld for legal reasons. Even when complete records are provided, questions may remain unanswered due to the lack of a standardized and required data set for all pregnant women. These problems, currently faced by all state maternal mortality review committees, highlight the need for some standardization of the processes for data collection and review of maternal death across all state jurisdictions. We would extrapolate that such national collective evidence could lead to more evidence-based consensus guidelines for prevention and intervention that can be tested and refined over time through continued efforts to monitor patterns and trends.

In their paper on pregnancy-related mortality in the US, Berg et al. [1], state that while the CDC can conduct nationwide surveillance on trends in maternal death, state-based reviews are needed to provide data to determine causes and develop protocol to meet the original target of Goal 5 of the United Nations Millennium Summit of September 2000 [14] of decreasing maternal mortality by 75 % by 2015. State-based review teams offer a useful resource for understanding the circumstances of each death. These collaborative efforts of Florida and Virginia endeavor to lower the risk of pregnancy-related mortality. We conclude that combining findings from state-based reviews of all maternal deaths using systematic data collection methods will lead to the identification of risk factors and provide the mechanism to develop specific interventions to address those risks. This may lead to reductions in pregnancy-related deaths in the United States as has been demonstrated through maternal death review and resultant guideline development and promulgation in the United Kingdom.

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