MATERNAL MORTALITY

DEATHS OF WOMEN DURING PREGNANCY, CHILDBIRTH AND WITHIN ONE YEAR AFTER PREGNANCY

ALBERTA, 1998 TO 2011

2014
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Maternal Mortality

Deaths of women during pregnancy, childbirth and within one year after pregnancy

ALBERTA, 1998-2011

Provincial Perinatal Quality Assurance Subcommittee & Maternal Mortality Working Group

Edited by Grace Guyon, Betty Jennissen, Michael Bow and Sharon Zhang

This report is dedicated to the memory of the women who died and their families.

The Alberta Medical Association Maternal-Welfare Committee & Committee on Reproductive Care in their commitment to improving the welfare of women in pregnancy and childbirth in Alberta established the foundation for this work to continue.

“A plea is made for the continuation of the vigilant Maternal Mortality Committees and allusion is made to their part in the decrease and prevention not only of maternal, but also of perinatal deaths.” J. Ross Vant, MD. The contribution made by maternal mortality committees. Canada. CMAJ. 1960; 82.
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Highlights of Results

- In Alberta from 1998-2011, there were 158 women identified as having died during pregnancy, childbirth or within one year after delivery. The mortality ratio was 25.42 per 100,000 deliveries for all causes of death. Of these, 64 women died of direct or indirect obstetric causes (51 deaths were classified as maternal deaths and 13 as late maternal deaths). Coincidental and unspecified or undetermined causes of deaths accounted for the death of 94 women in this population.

- The Alberta maternal mortality ratio (MMR) for direct plus indirect obstetric deaths for 1998-2011 was 8.21 (CI 6.11-10.7) per 100,000 deliveries. This rate is comparable to the national MMR of 8.6 (CI: 7.7-10.4) per 100,000 deliveries reported by the Public Health Agency of Canada in 2013.

- Risk of maternal death was higher with maternal age over 39 years and with parity of 5 or greater. The Public Health Agency of Canada (2013) reported that the MMR for women over 40 was 3.6 times (95% CI: 2.1-6.0) the rate experienced by women aged 20-24 years.

- The most common direct obstetrical causes of maternal deaths in Alberta were thromboembolism, amniotic fluid embolism and obstetric hemorrhage.

- The most common causes of indirect obstetrical maternal deaths in Alberta were cardiovascular disease, infectious diseases and suicide.

- The most common causes of coincidental death in Alberta were injury due to motor vehicle collisions and other medical conditions, including cardiac events and cancer.

- Most of the deaths from drug toxicity occurred after the puerperium (>42 days and within one year after pregnancy).

- Section 4 of the report includes expanded information on principle causes of deaths based on case scenarios, shared learning and targeted recommendations for management.

- Obesity was identified as a risk factor in maternal mortality cases from venous thromboembolism, cardiac diseases, infection, hemorrhage, amniotic fluid embolism and preeclampsia. Weight and BMI were not available for all cases reviewed.
Quality Improvement Opportunities from Shared Learning

- Provide preconception/prenatal counselling regarding:
  - risk of delayed childbearing
  - benefits of establishing weight within optimal BMI prior to conception
  - ideal weight gain in pregnancy
  - optimal management and specialist referral for chronic and acute medical conditions, including hypertension, diabetes, cardiovascular disease, thromboembolism, seizure disorders, other medical and mental health conditions
  - screening and referral for risk of substance misuse, mental health disorders, suicide and domestic violence

- Counsel women about prevention of infectious disease in pregnancy and offer influenza vaccination.

- Investigate persistent symptoms common in pregnancy as these may be an indication of other diseases or exacerbation of existing medical conditions, such as cancer, asthma, seizure and endocrine disorders.

- Engage multidisciplinary team(s) for care of pregnant women with complex medical and mental health conditions.

- Heighten awareness of the increased risk to pregnant women of adverse events when presenting to emergency departments with signs of illness: influenza, respiratory symptoms, and exacerbation of chronic illness, such as asthma, and risk for venous thromboembolism.

- Monitor for therapeutic levels of medications which may be impacted by pregnancy.

- Refer women “at risk” to community services during pregnancy and post-partum for grief and/or mental health counselling, addictions, domestic violence and financial assistance.

- Enhance and/or develop collaborative strategies for improving services to disadvantaged women in hospital and the community.

- Increase awareness that, in Alberta according to the Fatality Inquiries Act. (Revised Statutes of Alberta 2000 Chapter F-9. Current June 12, 2013) a medical examiner (OCME) must be notified of any maternal death that occurs during or following pregnancy that might be reasonably related to the pregnancy. Consent is not required by the OCME for autopsy.
  - If the OCME determines that an investigation into the death is necessary, then the OCME will accept the case. When a death is investigated by the OCME, it does not assure that an autopsy will be performed as part of the investigation to determine the cause of death and the manner of death.
  - Consent for a hospital medical autopsy must be obtained from next of kin in the event that the OCME does not authorize an autopsy. This autopsy would be performed by AHS Laboratory Services. The pathologist will accept or may decline the autopsy.
Introduction

World wide efforts towards improving maternal health are being made in response to the Millennium Development Goals (MDGs). Two targets for MDG 5 are reducing the maternal mortality ratio and achieving universal reproductive health care. Globally in 2010, an estimated 287,000 maternal deaths occurred; this is a 47% decline from the number of deaths in 1990 [1]. The estimates of maternal mortality ratio in the WHO (2012) document reports the maternal mortality ratio for developed regions as 16 per 100,000 live births. Beyond the Numbers (WHO, 2004) describes maternal death audit as one approach for ascertaining causes and contributing factors for maternal deaths and ill health [2].

The mortality surveillance cycle has been adopted internationally to review maternal deaths and to make pregnancy safer [3,4]. This is the ongoing cycle of identifying cases, collecting data, analyzing data, using the data to formulate recommendations for action, and evaluating the outcome. The ultimate purpose of the surveillance process is action. All steps in the process are required and important in order to enhance maternal and newborn care.

Diagram 1: Surveillance cycle
In Alberta a provincial quality assurance review of maternal deaths was initiated in 1936 by the Maternal Welfare Committee of the Alberta Medical Association (AMA) and subsequently by the AMA Committee on Reproductive Care. In 2012, the work of the AMA committee transitioned to the Alberta Health Services (AHS) Provincial Perinatal Quality Assurance Subcommittee (PPQA-SC) operating under the Alberta Perinatal Health Program (APHP). The Maternal-Welfare Committee and the AMA Committee on Reproductive Care reviewed deaths of women during pregnancy, childbirth and up to 90 days post-partum.

The Maternal Mortality Working Group (MMWG) of the PPQA-SC was established to complete a quality assurance review of deaths of women during pregnancy, childbirth and up to one year after pregnancy. The data is reported for all causes of deaths which include: maternal deaths (direct and indirect obstetric), late maternal deaths and coincidental and unspecified deaths. Analysis will include principle cause of death followed by discussion of key topics with the inclusion of several case studies highlighted to reinforce best practice and shared learning. In the presentation of case studies all efforts have been made to protect the identity of the women who died. Outcomes of this review will determine the feasibility of expanding the scope of monitoring, surveillance and quality assurance review of maternal mortality in Alberta to include up to one year after pregnancy. A commitment to act upon the recommendations in this report is a step towards improving maternal health and perinatal outcomes of childbearing women in Alberta.

**Purpose**

1. To identify factors associated with deaths of women during pregnancy, childbirth, and within one year after pregnancy with a view to mitigating factors and improving service delivery to women of childbearing age.

2. To share learning and opportunities for quality improvement in the delivery of care to women of childbearing age in Alberta.

3. To apply the WHO definitions of deaths during pregnancy, childbirth and the puerperium according to “The WHO Application of ICD-10 to deaths during pregnancy, childbirth and the puerperium: ICD-MM” [5].
Definitions and Terms

Deaths during pregnancy, childbirth and the puerperium\(^1\): Death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the cause of death (obstetric and non-obstetric). The term puerperium refers to the time period from childbirth to 42 days postpartum or post abortion [5, 6].

Maternal death\(^1\): Death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or the management, but not from accidental or incidental causes. Maternal deaths are either direct or indirect obstetric deaths.

   **Direct obstetric death:** Death resulting from obstetric complications of the pregnancy state (pregnancy, delivery, postpartum), from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above.

   **Indirect obstetric death:** Death resulting from previous existing disease or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by physiologic effects of pregnancy.

Late maternal death\(^1\): Death of a woman from direct or indirect causes more than 42 days but less than one year after termination of pregnancy.

**Coincidental death:** Death during pregnancy, childbirth or within one year after pregnancy due to external causes.

**Unspecified death:** Death during pregnancy, childbirth or within one year after pregnancy where the underlying cause is unknown or undetermined.

**Maternal Mortality Ratio (MMR):** The number of maternal deaths (direct + indirect) per 100,000 live births or per 100,000 deliveries in a given time period [5, 6]. The MMR expresses obstetric risk, or a woman’s chances of dying from a given pregnancy. This is the most commonly used indicator of maternal health and is used for international comparison. In developed countries the MMR is calculated using deliveries as the denominator. The denominator for the Alberta maternal mortality ratio is deliveries, unless otherwise stated.

**Deliveries:** Deliveries is used in reference to the number of live births + stillbirths as defined by Alberta Vital Statistics Act: Statutes of Alberta, 2007-Chapter V-4.1. Queens Printer, 2012.

**Termination of Pregnancy:** Termination in the WHO definitions and in this document refers to the end of the pregnancy or after pregnancy and may not be specific to but includes elective termination of pregnancy, spontaneous abortion and ectopic pregnancy [5].

\(^1\) The WHO Application of ICD-10 to deaths during pregnancy, childbirth and the puerperium: ICD-MM. 2012. WHO Department of Reproductive Health and Research, World Health Organization
Methodology

Ascertainment of Cases

Historically in Alberta, the provincial review of maternal mortality by the Alberta Medical Association included deaths during pregnancy, childbirth and up to 90 days post pregnancy. Past reports classified maternal deaths according to: A guide for maternal death studies. 1964. Council on Medical Service American Medical Association. The Provincial Perinatal Quality Assurance Subcommittee formed the Maternal Mortality Working Group to review and classify all deaths of women occurring in Alberta while pregnant or within one year after pregnancy between January 1, 1998 and December 31, 2011. An outcome of this inquiry would align classification of maternal deaths in Alberta with the WHO Application of ICD-10 to deaths during pregnancy, childbirth and the puerperium: ICD-MM [5] and will establish a baseline for further reporting.

As a result of broadening the criteria for this review, the first step in the process was to ascertain all deaths occurring in the province from January 1, 1998 to December 31, 2011 which met the criteria. Previous to this inquiry 65 cases had been ascertained and reviewed by the AMA Committee on Reproductive Care. An additional 93 cases meeting the criteria for the expanded review were identified through information received from Alberta Health Services (AHS) Health Information Management, Alberta Vital Statistics, the Office of the Chief Medical Examiner (OCME) and AHS Data Integration, Measurement and Reporting (DIMR). Of the women included in this inquiry, seven had a primary address with an out-of-province postal code.

Once confirmation of a pregnancy was made the appropriate case documentation was requested to assist with completion of the review by the working group.

The OCME assisted in validating cases of maternal deaths in the community. The AHS DIMR accessed inpatient information based on ICD-10 coding back to 2002 and emergency visits back to 2008 to identify women who died within a year of delivery, miscarriage, pregnancy termination or receiving pregnancy inpatient care at an AHS facility. Due to the limitations of DIMR access to data in earlier years, as well as challenges in identifying deaths in the community that fit the criteria for inquiry, the number of deaths of women in pregnancy, childbirth, the puerperium and up to one year after pregnancy regardless of the cause of death in Alberta is likely to have been under-reported.
Review Process

All deaths occurring in Alberta while pregnant or within one year after pregnancy between January 1, 1998 and December 31, 2011 that could be ascertained were included in this review. The PPQA-SC and MMWG members included perinatologists, obstetricians, family physicians, midwives, pathologists, nurses and specialists in the field of internal medicine, anaesthesiology and psychiatry who hold an interest in the field of obstetrics and perinatal health. The MMWG is a multidisciplinary group of practitioners, including specialists invited to attend the inquiry depending on the nature of the case being presented. In addition to the PPQA-SC and MMWG members, other specialists were invited to author specific topics in the report and/or to validate the information provided specific to their expertise and areas of interest. Participants of the MMWG as well as those contributing their expertise are listed at the beginning of this report.

A review was completed of each death by a working group member and presented to the MMWG. For each death, data was collected by the MMWG on a standard form including information concerning general health and obstetric histories for the index pregnancy. Sources of information included the prenatal record, delivery record, laboratory reports, operative reports, consultations, medical examiner autopsies and medical examiner summaries. Each death was classified according to the WHO application of ICD-10 coding of deaths during pregnancy, childbirth and the puerperium [5]. Outcomes of the reviews were presented to the PPQA-SC for validation of classification and recommendations.

Limitations

It is not possible to say with confidence that all deaths of women during pregnancy or within one year after pregnancy from 1998 to 2011 were identified through the ascertainment process for this inquiry. There is greater confidence in having identified deaths during pregnancy, childbirth and the puerperium than in the late maternal and coincidental deaths. Late maternal and coincidental deaths often occur in the community and the women who died may not have been admitted to hospital. In some circumstances a pregnancy or birth may not have been disclosed. The review process was retrospective and for some deaths it was difficult to collect information back 14 years. The case material in the review process focused on the incident that lead to the woman’s death and may not have been complete in overall assessment of maternal health or the totality of care provided. Medical examiner autopsy or external examination summary was released for 80.7% of medical examiner cases; 24.7% of all deaths reviewed were not determined to be a medical examiner case, of these two had a hospital autopsy.

The collaboration with DIMR aided in the retrieval of many new cases from 2002. It is however, correct to say that the figures from this inquiry may still be an underestimate of the deaths of women during pregnancy, childbirth or within one year post pregnancy in Alberta.

At times the MMWG found it challenging to determine whether diagnosis and treatment may have been affected by the woman’s pregnancy. It was found that classifying some deaths according to the WHO ICD-10 was a subjective process that could be influenced by the committee membership.
Section 1: Population

In Alberta, from January 1, 1998 to December 31, 2011, 158 women were determined to have died in pregnancy, childbirth or within one year after a pregnancy. There were 621,402 deliveries in Alberta from 1998 to 2011. Of the 158 women in this inquiry, 151 were Alberta residents and 7 were non-residents.

Diagram 2: Population
Ethnicity and Migrant Status of Alberta Residents

In the process of the review of the deaths of women in the population who were residents of Alberta, the MMWG had questions about the ethnicity of the woman who died. There were concerns that disadvantaged women may be over-represented. Information on ethnicity was not consistently recorded on the standardized Alberta prenatal record and is not a component of the Alberta Vital Statistics Birth Registration.

In an attempt to respond to the MMWG inquiry, the assistance of Customer Relationship Management (CRM) and Data Access Information and Analysis, Strategic Services at Alberta Health was requested. As a result of this consultation, aggregate data on the ethnicity and migrant status of women who died in this population who were Alberta residents during 1998 – 2011 was established [7]. The overall population of Alberta resident deaths (n=151) in this review were linked to a First Nations Registry, Immigrant Registry, South Asian and validated Chinese surname list. The Alberta Immigrant Registry includes individuals applying for health care coverage for the first time (i.e. just moving to Alberta). The Alberta Immigrant Registry uses the Alberta Health Care Insurance Plan Central Stakeholder Registry (CSR) to identify people who have migrated into Alberta since 1984. Immigration information, such as country or province of origin and date of arrival is typically provided when people register for health care coverage under the Alberta Health Care Insurance Plan (AHCIP). The CSR does not capture secondary migration. This means that if someone immigrated to Canada and lived in another province for a period of time prior to moving to Alberta, they were considered an interprovincial migrant. The number of deaths were counted and tabulated by migration status (international immigrants, interprovincial migrants, unknown status of migration, and non-migrants), and ethnic group (Caucasians, First Nations, Chinese, South Asians, and others). Due to the small number of cases for most ethnic groups, the final output table included four groups for ethnicity: Caucasians, First Nations, South Asians and others.

In future reviews of maternal deaths, it would be valuable to have the ethnicity of individual women for a comprehensive analysis of factors associated with the death of women during pregnancy or within one year after pregnancy.

Calculating maternal mortality ratios related to ethnicity was not possible in Alberta as the denominator for the number of deliveries among each ethnic population was not available. Health Canada (2013), reported a maternal mortality ratio for First Nations women from 2001 to 2011 as 5.7 per 100,000 deliveries during some phase of childbearing [8]. The proportion of First Nations among live births in Alberta was 7.1% between 2005 and 2011².

² Data source First Nations Registry and Vital Statistics Live Birth Registry
The ethnicity of the largest percent of Alberta residents of women in this review were Caucasian (66.2%, n=100). First Nations women made up the second largest proportion (22.5%, n=34) of women who died in Alberta while pregnant or within one year after pregnancy. Refer to Table 1.

Table 1: Ethnicity - Alberta Residents, 1998 – 2011

<table>
<thead>
<tr>
<th>Ethnic Group*</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasians</td>
<td>100</td>
<td>66.2</td>
</tr>
<tr>
<td>First Nations</td>
<td>34</td>
<td>22.5</td>
</tr>
<tr>
<td>South Asians</td>
<td>10</td>
<td>6.6</td>
</tr>
<tr>
<td>Others /Unknown</td>
<td>7</td>
<td>4.6</td>
</tr>
</tbody>
</table>

In this review, 61.6% of the deaths of Alberta women were non-migrants. International immigration accounted for 13% of the Alberta women. Thirteen percent of the overall population were interprovincial immigrants and 13% had an unknown migrant status. Given the diverse immigrant populations in Alberta, as well as variations in health and lifetime of exposure to risk factors in other parts of the world, it is important to ensure effective and ongoing monitoring of the health of immigrant mothers in Alberta [7]. Refer to Table 2.

Table 2: Migrant Status of Alberta Residents, 1998 - 2011

<table>
<thead>
<tr>
<th>Migrant Status</th>
<th>Deaths (n)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-migrants</td>
<td>93</td>
<td>61.6</td>
</tr>
<tr>
<td>International immigrants</td>
<td>20</td>
<td>13.3</td>
</tr>
<tr>
<td>Interprovincial immigrants</td>
<td>19</td>
<td>12.6</td>
</tr>
<tr>
<td>Status Unknown migrants</td>
<td>19</td>
<td>12.6</td>
</tr>
</tbody>
</table>

Note:
1. The migrant status is derived from the Immigrant Registry, with unknown migrant status corrected.
2. The ethnic group status is derived from the First Nations Registry, together with the list of South Asians, Chinese and other ethnic groups. The ethnic group is a combination of First Nations Registry, South Asians, and validated Chinese Surname list.

Produced by: CRM & Data Access, Strategic Services, Alberta Health
Mortality Ratio by Classification of Death

The mortality ratio for all women who died during pregnancy, childbirth or within one year of pregnancy for all causes of death was 25.4 per 100,000 deliveries. Refer to Table 3.

Table 3: Mortality Ratio by Classification of Death - Alberta, 1998-2011

<table>
<thead>
<tr>
<th>Classification</th>
<th>Deaths (n)</th>
<th>% total deaths N=158</th>
<th>Ratio per 100,000 Deliveries N= 621,402</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td>51</td>
<td>32.28</td>
<td>8.21</td>
</tr>
<tr>
<td>Late Maternal</td>
<td>13</td>
<td>8.22</td>
<td>2.09</td>
</tr>
<tr>
<td>Sub-total</td>
<td>64</td>
<td>40.51</td>
<td>10.30</td>
</tr>
<tr>
<td>Coincidental</td>
<td>86</td>
<td>54.43</td>
<td>13.84</td>
</tr>
<tr>
<td>Unspecified</td>
<td>8</td>
<td>5.06</td>
<td>1.29</td>
</tr>
<tr>
<td>Total mortality Ratio</td>
<td>158</td>
<td>100</td>
<td>25.42</td>
</tr>
</tbody>
</table>

Mortality Ratio by Maternal Age

Women 40 years and older who died during pregnancy or within one year of pregnancy for all causes of death had a significantly higher mortality rate than for women 25 to 34 years of age. Refer to Table 4.

Table 4: Mortality Ratio by Maternal Age – Alberta, 1998 - 2011

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Deaths (n)</th>
<th>Deliveries (n)</th>
<th>Mortality Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>13</td>
<td>33835</td>
<td>38.42</td>
<td>20.46-65.69</td>
</tr>
<tr>
<td>20 - 24</td>
<td>37</td>
<td>118004</td>
<td>31.35</td>
<td>22.08-43.22</td>
</tr>
<tr>
<td>25 - 29</td>
<td>35</td>
<td>195669</td>
<td>17.89</td>
<td>12.46-24.88</td>
</tr>
<tr>
<td>30 - 34</td>
<td>38</td>
<td>178185</td>
<td>21.33</td>
<td>15.09-29.27</td>
</tr>
<tr>
<td>35 - 39</td>
<td>25</td>
<td>78926</td>
<td>31.68</td>
<td>20.50-46.76</td>
</tr>
<tr>
<td>40 years and older</td>
<td>10</td>
<td>15049</td>
<td>66.45</td>
<td>31.87-122.17</td>
</tr>
</tbody>
</table>
Gestational Age of Pregnancy by Classification of Death

Of the women who died during pregnancy, childbirth and within one year post delivery 60.1% did not reach 37 completed weeks of pregnancy. Refer to Table 5.

Table 5: Gestational Age of Pregnancy by Classification – Alberta, 1998 - 2011

<table>
<thead>
<tr>
<th>Gestation Weeks</th>
<th>Total (n)</th>
<th>Maternal</th>
<th>Coincidental /Unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Direct</td>
<td>Indirect</td>
</tr>
<tr>
<td>≤20</td>
<td>43</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>21 - 23</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>24 - 27</td>
<td>11</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>28 - 36</td>
<td>34</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>&gt;37</td>
<td>63</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Not reported</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>158</td>
<td>23</td>
<td>28</td>
</tr>
</tbody>
</table>

Perinatal Outcome

Of the women who died, 50.6% had a live birth compared to 27.8% who experienced a perinatal loss (fetal or neonatal death) during childbirth or termination of pregnancy. Of the women who died, 21.5% were pregnant at the time of death. Refer to Table 6.

Table 6: Perinatal Outcome - Alberta, 1998–2011

<table>
<thead>
<tr>
<th>Perinatal Outcome</th>
<th>Population n =158</th>
<th>% of population</th>
<th>Maternal Deaths n = 51</th>
<th>% Maternal Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant at time of death</td>
<td>34</td>
<td>21.5</td>
<td>15</td>
<td>29.4</td>
</tr>
<tr>
<td>Live Birth</td>
<td>80</td>
<td>50.6</td>
<td>23</td>
<td>45.1</td>
</tr>
<tr>
<td>Abortion</td>
<td>26</td>
<td>16.4</td>
<td>8</td>
<td>15.6</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>8</td>
<td>5.0</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>Neonatal Death</td>
<td>10</td>
<td>6.3</td>
<td>3</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Abortion: includes perinatal loss from spontaneous abortion, termination of pregnancy & ectopic pregnancy

Maternal Mortality: Deaths of Women During Pregnancy, Childbirth and Within One Year After Pregnancy in Alberta, 1998 to 2011
Section 2: Maternal & Late Maternal Deaths

This section of the report compares Alberta’s maternal mortality ratio to Canada’s; presents trends in Alberta maternal mortality ratios from 1998 to 2011 and analysis of data on mothers who died during pregnancy, childbirth or the puerperium from direct and indirect obstetric causes. Principle cause of direct and indirect obstetrical causes are presented for maternal and late maternal deaths. Refer to Table 10 & Table 11. There were 51 maternal deaths and 13 late maternal deaths identified in Alberta from 1998-2011. Of these, two were non-residents that received care and died in Alberta.

Maternal Mortality Ratio

The term “maternal death” is used specifically for direct and indirect obstetric causes of deaths during pregnancy, childbirth and the puerperium (< 42 days post pregnancy). The maternal mortality ratio (MMR) includes direct + indirect deaths per 100,000 deliveries. The Public Health Agency of Canada (2013) reports the national MMR from 1997/1998 to 2010/11 fiscal year to be 8.6 (95% CI: 7.7-9.6) per 100,000 deliveries in Canada (excluding Quebec) [9]. The Alberta MMR was reported as 7.9 (95% CI: 5.8 -10.4) in the Public Health Agency of Canada Report. The maternal mortality ratio (MMR) in Alberta for the 1998 – 2011 calendar years in this inquiry was 8.21 per 100,000 deliveries (95% CI: 6.11-10.79). Late maternal deaths from direct and indirect causes are not included in calculating the MMR.

Due to small numbers of cases, there is no clear trend in maternal mortality ratios identified in Alberta by 2 year combined time frames for 1998-2011. Refer to Figure 1:

Figure 1: Trends in Maternal Mortality Ratio per 100,000 deliveries in Alberta, 1998-2011

<table>
<thead>
<tr>
<th>Year</th>
<th>MMR</th>
<th>Direct MMR</th>
<th>Indirect MMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998/1999</td>
<td>7.81</td>
<td>3.91</td>
<td>3.91</td>
</tr>
<tr>
<td>2000/2001</td>
<td>7.87</td>
<td>3.94</td>
<td>3.94</td>
</tr>
<tr>
<td>2002/2003</td>
<td>8.69</td>
<td>3.72</td>
<td>4.96</td>
</tr>
<tr>
<td>2004/2005</td>
<td>8.28</td>
<td>3.55</td>
<td>4.73</td>
</tr>
<tr>
<td>2008/2009</td>
<td>12.5</td>
<td>7.69</td>
<td>4.81</td>
</tr>
<tr>
<td>2010/2011</td>
<td>5.80</td>
<td>0</td>
<td>5.80</td>
</tr>
</tbody>
</table>
Direct and Indirect Obstetric Deaths

In Alberta, from 1998 to 2011 there were 51 women identified who died from direct or indirect obstetric causes during pregnancy, childbirth and the puerperium. Of these, 23 maternal deaths were classified as direct obstetric deaths. The direct obstetric MMR was 3.70 per 100,000 deliveries. There were 28 maternal deaths classified as indirect obstetric deaths. The indirect obstetric MMR was 4.51 per 100,000 deliveries. Refer to Table 10 for principle cause of maternal deaths during pregnancy, childbirth and the puerperium.

Table 7: Maternal Mortality Ratio, Alberta 1998 – 2011

<table>
<thead>
<tr>
<th>Classification</th>
<th>Maternal Deaths</th>
<th>MMR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Obstetric</td>
<td>23</td>
<td>3.70</td>
<td>2.35-5.55</td>
</tr>
<tr>
<td>Indirect Obstetric</td>
<td>28</td>
<td>4.51</td>
<td>2.99-6.51</td>
</tr>
<tr>
<td>Total Maternal Deaths</td>
<td>51</td>
<td>8.21</td>
<td>6.11-10.79</td>
</tr>
</tbody>
</table>

Maternal Mortality Ratio by Maternal Age

The age range of women was 19 to 45 years of age at the time of death with a mean age of 30 years. The MMR increased in the over 35 age group and increased dramatically in the over 40 age group. The Public Health Agency of Canada (2013) reported that the MMR for women over 40 was 3.6 times (95% CI: 2.1-6.0) the rate experienced by women aged 20-24 years.

Table 8: Maternal Mortality Ratio by Maternal Age, 1998 – 2011

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Deaths (n)</th>
<th>Deliveries (n)</th>
<th>MMR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1</td>
<td>33835</td>
<td>2.96</td>
<td>0.075-16.47</td>
</tr>
<tr>
<td>20 - 24</td>
<td>9</td>
<td>118004</td>
<td>7.63</td>
<td>3.49-14.48</td>
</tr>
<tr>
<td>25 - 29</td>
<td>14</td>
<td>195669</td>
<td>7.15</td>
<td>3.91-12.00</td>
</tr>
<tr>
<td>30 - 34</td>
<td>12</td>
<td>178185</td>
<td>6.73</td>
<td>3.48-11.76</td>
</tr>
<tr>
<td>35 - 39</td>
<td>10</td>
<td>78926</td>
<td>12.67</td>
<td>6.08-23.30</td>
</tr>
<tr>
<td>40 + years</td>
<td>5</td>
<td>15049</td>
<td>33.22</td>
<td>10.79-77.52</td>
</tr>
</tbody>
</table>
Maternal Mortality by Parity

The MMR was higher with a parity of five and greater.

Table 9: Maternal Mortality Ratio by Parity, 1998 – 2011

<table>
<thead>
<tr>
<th>Parity</th>
<th>Deaths (n)</th>
<th>MMR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous</td>
<td>18</td>
<td>6.83</td>
<td>4.05-10.8</td>
</tr>
<tr>
<td>Multiparous</td>
<td>29</td>
<td>8.19</td>
<td>5.49-11.76</td>
</tr>
<tr>
<td>1-4</td>
<td>26</td>
<td>7.49</td>
<td>4.96-11.12</td>
</tr>
<tr>
<td>5 and greater</td>
<td>3</td>
<td>26.40</td>
<td>5.44-77.12</td>
</tr>
</tbody>
</table>

Note: Parity for 4 cases was not documented

Late Maternal Deaths

In Alberta from 1998 – 2011, there were 13 late maternal deaths (deaths > 42 days and within one year after pregnancy) reported. These were all classified as indirect obstetric deaths. Table 11 shows the principle cause of late indirect maternal deaths. Over half of the late indirect maternal deaths (n=7) were from suicide. The women who died as a result of suicide ranged in age from 17 to 38 years with a mean age of 24 years at the time of death. Factors such as a history of depression, previous suicide attempts, substance misuse, domestic violence and perinatal loss were documented. Two indirect late maternal deaths were from drug toxicity, the information available does not indicate whether the drug overdose was intentional. Two cases of cerebral bleed and one case each of cancer and a cardiac incident complete the late indirect death category. Refer to Table 11.
Principle Cause of Maternal Deaths

The most common principle causes of direct obstetrical deaths were venous thromboembolism and amniotic fluid embolism; whereas cardiovascular disease, infectious disease, and suicide were the most common causes of indirect obstetric deaths. Refer to Figure 2, Table 10 & Table 11. Obesity was identified as a risk factor in several deaths where maternal weight or BMI was documented. The national report recently produced by the Public Health Agency of Canada (2013), cites the leading cause of maternal death as cardiovascular diseases.

**Maternal death by suicide**

The WHO application of ICD-10 coding to deaths during pregnancy, childbirth and the puerperium: 1CD-MM, 2012 [5] recommends that deaths due to suicide be classified as direct maternal deaths. The recommendations apply even if it is not possible to definitively establish the diagnosis of puerperal psychosis and/or postpartum depression. In past years suicides were classified as incidental maternal deaths. The MMWG classified deaths by suicide as indirect obstetric deaths; this is in keeping with the Center for Maternal and Child Enquires in the UK and the Perinatal and Maternal Mortality Review Committee of New Zealand [3, 12]. The majority of deaths in Alberta due to suicide occurred in the community. It was very difficult to obtain past and current medical history to determine if mental illness was a concern in pregnancy or postpartum.

Figure 2: Principle Cause of Maternal Death in Alberta, 1998 - 2011
### Table 10: Principle Cause of Maternal Death in Alberta, 1998 - 2011

<table>
<thead>
<tr>
<th>Direct Obstetric Deaths</th>
<th>n</th>
<th>MMR per 100,000 Deliveries</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous Thromboembolism</td>
<td>8</td>
<td>1.29</td>
<td>0.56-2.54</td>
</tr>
<tr>
<td>Amniotic Fluid / Air Embolism</td>
<td>5</td>
<td>0.80</td>
<td>0.26-1.88</td>
</tr>
<tr>
<td>Obstetric Hemorrhage</td>
<td>3</td>
<td>0.48</td>
<td>0.10-1.41</td>
</tr>
<tr>
<td>Ectopic Pregnancy</td>
<td>2</td>
<td>0.32</td>
<td>0.04-1.16</td>
</tr>
<tr>
<td>Pre-eclampsia / Eclampsia</td>
<td>2</td>
<td>0.32</td>
<td>0.04-1.16</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>2</td>
<td>0.32</td>
<td>0.04-1.16</td>
</tr>
<tr>
<td>Anaesthesia Related</td>
<td>1</td>
<td>0.16</td>
<td>0.04-1.16</td>
</tr>
<tr>
<td><strong>Total Direct Obstetric Deaths</strong></td>
<td>23</td>
<td>3.70</td>
<td>2.35-5.55</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indirect Obstetric Deaths</th>
<th>n</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Disease</td>
<td>9</td>
<td>1.45</td>
<td>0.66-2.75</td>
</tr>
<tr>
<td>Infectious Disease</td>
<td>6</td>
<td>0.80</td>
<td>0.26-1.88</td>
</tr>
<tr>
<td>Suicide</td>
<td>5</td>
<td>0.80</td>
<td>0.26-1.88</td>
</tr>
<tr>
<td>Other Medical Disorders</td>
<td>4</td>
<td>0.80</td>
<td>0.26-1.88</td>
</tr>
<tr>
<td>Idiopathic epilepsy</td>
<td>3</td>
<td>0.48</td>
<td>0.10-1.41</td>
</tr>
<tr>
<td>Drug Toxicity</td>
<td>1</td>
<td>0.16</td>
<td>0.04-1.16</td>
</tr>
<tr>
<td><strong>Total Indirect</strong></td>
<td>28</td>
<td>4.51</td>
<td>2.99-6.51</td>
</tr>
</tbody>
</table>

| Total Maternal Deaths – Direct & Indirect | 51| 8.21                      | 6.11-10.79 |

### Table 11: Principle Causes of Late Maternal Death in Alberta, 1998 – 2011

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide</td>
<td>7</td>
</tr>
<tr>
<td>Cerebral bleed</td>
<td>2</td>
</tr>
<tr>
<td>Drug Toxicity</td>
<td>2</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>13</td>
</tr>
</tbody>
</table>
Section 3: Coincidental & Unspecified Deaths due to external causes or cause unknown or undetermined

Coincidental deaths

The coincidental deaths of women make up the largest portion of deaths reviewed by the MMWG. Of the 86 deaths reported, coincidental deaths accounted for 34 deaths of women during pregnancy and the puerperium; whereas 56 deaths occurred at more than 42 days and less than one year after pregnancy. The three leading causes of coincidental deaths in this population of women were cancer, drug toxicity and motor vehicle collisions. Twenty-four percent (n=21) of the coincidental deaths were the result of cancer. Twenty-two percent were from drug toxicity (n=19) and 22% were a result of motor vehicle collisions (n=19). The mortality ratio for coincidental deaths was 13.88 per 100,000 deliveries.

Table 12: Principle Causes of Coincidental Deaths in Alberta, 1998-2011

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Pregnant</th>
<th>≤42 days post-pregnancy</th>
<th>&gt; 42 but ≤365 days post-pregnancy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Toxicity</td>
<td>1</td>
<td>2</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Homicide</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Cancer</td>
<td>0</td>
<td>4</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>Motor Vehicle Deaths</td>
<td>9</td>
<td>6</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Other Medical Conditions, including:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cardiac, cerebral bleed, seizure disorder, endocrine disease, fat emboli, GI and liver disease and other medical conditions</td>
<td>3</td>
<td>4</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>17</td>
<td>52</td>
<td>86</td>
</tr>
</tbody>
</table>
Motor vehicle deaths

Motor vehicle collisions are preventable causes of trauma in pregnancy. Seat belts are a first line of defence in a collision. In two deaths restraints were used, in one death restraints were not used, and in six deaths use of restraint is not known. Two cases involved a pedestrian and vehicle collision. Information positively influences seat belt use in pregnancy as pregnant women may be unsure of how to correctly wear a three point safety restraint and may believe it will harm their fetus [13,14,15]. Women who are counselled about proper use of seat belts were more inclined to wear them correctly [13, 16]. Whitehead (2011) found that slightly less than half (48.5%) of women who received prenatal care reported being counselled on using seatbelts during pregnancy. Proper use of seat belts is an important topic to address prenatally as when worn incorrectly association with fetal injury is reported. Alcohol, speed and road conditions were also factors in a number of cases of motor vehicle collisions reviewed in Alberta.

According to an analysis of the risk of a traffic crash with pregnant women as drivers, Redelmeier et al (2014) concluded that pregnancy is associated with a substantial risk of a serious motor vehicle accident during the second trimester and that this risk merits attention for prenatal care [17].

Unspecified

There were eight deaths in this category with cause of death undetermined. Seven of these deaths occurred during pregnancy, childbirth or the puerperium and one after 42 days but less than one year after pregnancy. The cause of death was undetermined by medical examiner autopsy. According to the medical examiner autopsy the manner of death in six of these women was of natural causes with the possibility of cardiac arrhythmia. One woman had acute liver failure of unknown cause.
References


Other Sources


Section 4: Clinical Causes of Death: Case Scenarios & Shared Learning

Venous Thromboembolism........................................................................................................27-30
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Cardiovascular Disease............................................................................................................53-59
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Cancer in Pregnancy .................................................................................................................69-81
MATERNAL MORTALITY DUE TO VENOUS THROMBOEMBOLISM IN ALBERTA 1998-2011

Paul S. Gibson, MD, FRCPC

Venous thromboembolism (VTE) is a leading cause of maternal mortality around the world, particularly in developed countries [1-4]. Developing countries, with less well developed medical systems and access to care, suffer from excess maternal mortality due to bleeding, infection, preeclampsia/eclampsia and obstructed labour [5-6]. In these countries VTE can also pose a significant risk. In countries with modern medical systems like Canada's, VTE has been at the top among causes of maternal death in recent decades - though in the most recent review from the UK the incidence of maternal mortality due to VTE was noted to decline significantly compared to prior reports[1]. This is postulated to be due, in part, to increased awareness of women at increased risk for VTE in pregnancy and targeted thromboprophylaxis. The overall incidence of VTE in pregnancy has been estimated to be ~ 1:1000 maternities [7]. Risk factors including: Cesarean delivery, increased age (>35), obesity, the presence of congenital or acquired thrombophilias, current smoking, immobility (i.e. bed rest, travel), black race, multiple gestation, underlying cardiac disease, preeclampsia, and early delivery (<36 weeks) have all been found to increase the risk of VTE in pregnancy [8].

Pregnancy-associated VTE is generally considered a DIRECT cause of maternal death. Direct maternal deaths are defined as “death resulting from complications of pregnancy itself, from interventions elected or required by the pregnancy, or resulting from the chain of events initiated by the complication or the intervention”. During the period of January 1, 1998 to December 31, 2011 there were 8 maternal deaths (during pregnancy or up to one year postpartum) due to VTE. Four of these occurred during pregnancy and the remaining four occurred within 1 month postpartum.

Maternal Deaths during Pregnancy (n=4)

There were four maternal deaths due to VTE which occurred during pregnancy. Three of these occurred during the first trimester (at 6, 8 and 9 weeks gestation) while the fourth occurred at approximately 25 weeks gestation. Of the first trimester maternal deaths due to VTE, one occurred at six weeks gestation (see Case Example #1) in a morbidly obese woman (BMI=59.2) who had received assisted reproductive technology in the form of clomiphene citrate for ovulation induction; one occurred at nine weeks gestation in a woman with hyperemesis gravidarum; the third death occurred at eight weeks gestation in a woman with a prior history of DVT who was not taking thromboprophylaxis; the remaining antepartum maternal death due to VTE was a sudden death at approximately 25 weeks gestation in a woman subsequently found to have extensive pulmonary emboli.
**Postpartum Maternal Deaths (n=4)**

Of the four maternal deaths which occurred postpartum, three occurred within four days of delivery. One occurred four days following a spontaneous vaginal delivery, one two days after an emergency Cesarean section during labour (see Case Example #2) and one within 24 hours of an elective Cesarean delivery. All three of these women with immediate postpartum deaths from VTE were overweight or obese, with BMIs ranging from 29 to 40. The remaining postpartum maternal death occurred approximately one month postpartum from an unattended vaginal delivery at home, in a woman also noted to be overweight.

**VTE- Case 1**

A greater than 30 year-old, obese woman (167 kg, BMI 59.2) achieved her first pregnancy via the use of clomiphene citrate and progesterone. At about six weeks gestation she experienced lower abdominal pain for a few days, followed by complaints of chest pressure and dyspnea accompanied by a syncope episode at home. She did not present to the hospital until the next afternoon. While waiting to be seen in emergency she developed increasing shortness of breath and cough, then was found to be mottled, cyanotic and pulseless. Resuscitation efforts were unsuccessful. Autopsy confirmed acute bilateral pulmonary emboli with right ventricular decompensation.

**VTE - Case 2**

A women between 20-25 years of age, G1 with obesity (103 kg, BMI 40), and no other significant past medical history presented in spontaneous labour at 41 weeks gestation. After approximately 13 hours she required an emergency low segment Cesarean section due to failure to progress in labour and maternal exhaustion. There were no immediate peri or postoperative complications and the neonate was fine. On the second postpartum day, while mobilizing on the postpartum ward, she developed abrupt dyspnea and hypotension and then collapsed in a pulseless electrical activity (PEA) cardiopulmonary arrest. Despite an initially successful resuscitation involving thrombolytic therapy, the woman suffered a severe hypoxic brain injury and care was withdrawn on postpartum day four. Autopsy confirmed pulmonary embolism.

**Discussion Points**

It is notable that of the four maternal deaths due to VTE which occurred in the antepartum period, three occurred during the first trimester. This finding illustrates that the hypercoagulability of pregnancy, and associated risk of potentially fatal DVT/PE, is clinically relevant by the middle of the first trimester. Given the potential to prevent VTE with effective thromboprophylaxis, women with a history of VTE or major current risk factors (obesity, immobilization, age, etc.) should have an individualized risk assessment and be considered for targeted thromboprophylaxis with low molecular weight heparin (LMWH) from the earliest stages of a confirmed pregnancy. The risk of VTE may be higher among some women following assisted reproductive therapies, particularly older women undergoing in-vitro fertilization (IVF) complicated by ovarian hyperstimulation syndrome.
Obesity is epidemic in western society and has been shown to be a major risk factor for multiple pregnancy complications, including: VTE, gestational diabetes, hypertension and preeclampsia. Of the women in this cohort with a known weight or BMI (known in 5/8 cases), all were either overweight or obese (BMI ranging from 29-59). In the most recent data from the UK (2006-8) [1], 78% of women who died of thrombosis/VTE were overweight (BMI of at least 25) and 61% were obese (BMI >= 30). This is a major concern, given the increasing population prevalence of obesity in pregnancy in recent years. The obese woman should have close clinical surveillance and/or thromboprophylaxis if there are additional VTE risk factors.

Cesarean delivery remains a major risk factor for postpartum VTE, particularly in women with additional risk factors. Current guidelines out of the UK [9] suggest that women should receive an individualized VTE risk assessment postpartum - and that women with risk factors should receive between 7-42 days of thromboprophylaxis. The implementation of these recommendations has coincided with a significant reduction in maternal mortality due to VTE in the UK.

**Shared Learning** - prevention of maternal deaths from venous thromboembolism

- Preconception counseling should include strong advice about weight reduction/optimization prior to pregnancy, in order to reduce risks (including VTE) in pregnancy.

- Upon conception (or pre-pregnancy) women should undergo an individualized VTE risk assessment - and be considered for antepartum thromboprophylaxis with LMWH in the setting of risk factors such as prior VTE, obesity, thrombophilia, immobility, and other risk factors.

- Women and health professionals should continue to be educated regarding the symptoms of DVT and PE, the necessity for prompt medical attention and investigation of concerning symptoms, and the safety of diagnostic and treatment modalities in pregnancy.

- Women should also be screened for their thrombotic risk during the peripartum interval, with a plan for targeted postpartum thromboprophylaxis of women at increased risk (post-Cesarean section, prior VTE plus or minus thrombophilia, obesity, immobilization, and other risk factors).
References


Obstetrical Hemorrhage

Obstetrical hemorrhage is a leading cause of maternal mortality, accounting for over 50% of maternal deaths worldwide. There is variability in reported trends in developed countries; the 2011 Confidential Enquiry into Maternal and Child Health (CEMACE) described a reduction in maternal deaths from obstetrical hemorrhage and attributed this to improved identification and management of at-risk patients [1]. Other reports have suggested the opposite trend in high income countries [2]. Although this finding may be surreptitious due to changes in reporting systems, increasing rates of Caesarean section, older maternal age and obesity in pregnancy may be contributing towards a real problem. Regardless, obstetrical hemorrhage is a serious and important contributor to maternal mortality and ongoing attention and quality improvement is deserved.

For this inquiry, diagnosis of obstetrical hemorrhage is reserved to those presenting at or beyond 20 weeks of gestational age. Death from pathologically confirmed amniotic fluid embolism (AFE) is categorized separately but recognition of an overlap in clinical presentation and subsequent management is made.

There were three direct maternal deaths from obstetrical hemorrhage reported in Alberta between 1998 and 2011. These cases involve both antepartum, intrapartum and post partum hemorrhage, but excluded those related to early pregnancy complications. However, it is important to recognize there were two deaths related to ectopic pregnancy, including one case with early aggressive resuscitation in a tertiary centre. This highlights the importance of remaining vigilant for the signs and symptoms of ectopic pregnancy in women of child bearing age and the need for rapid evaluation and appropriate medical attention with suspected ectopic pregnancy rupture.

As mirrored in the 2011 CEMACE report, complications from prior Caesarean section were not a prominent theme amongst maternal deaths in Alberta. However, it is appreciated that this review does not reflect potential severe morbidities that may have occurred in surviving partituen from adherent placenta or uterine rupture. Uterine atony remains a major cause of postpartum hemorrhage and was identified in two cases in this review, both following prolonged labours. In two cases, obstetrical hemorrhage was felt to be related to grand multiparity. In one case, death occurred prior to presentation at hospital and the woman had a history of >10 deliveries. She did not seek any obstetrical care. Few details could be ascertained on this case, but placental abruption was diagnosed at autopsy. The second case due to postpartum hemorrhage is described in detail below. There was one case of sudden death occurring in an
otherwise uncomplicated Caesarean delivery for placenta previa. The extremely rare cause of death was later determined to be from air embolism.

Other causes of death not directly related to obstetrical hemorrhage include an adverse anaesthetic reaction and amniotic fluid embolism. There was one case of a sudden cardiac death during a Caesarean section for which no significant risk factors or triggers were determined. Autopsy identified no apparent explanation for the event. As maternal mortality is a rare but catastrophic event, detailed review to ensure quality improvement and maintenance is essential. The cases discussed are with view to this.

**Obstetric Hemorrhage - Case 1**

A women in her thirties, G1P0 was induced at 37 weeks for preeclampsia. At 8 cm dilatation, she had an emergency Cesarean section for an abnormal fetal heart tracing and labour dystocia. Her pregnancy was further complicated by obesity (BMI not recorded but weight >105 kg), and gestational diabetes.

Although hemostasis was noted at the time of her delivery, the patient deteriorated in the recovery room, with reported hemoglobin of 48. Post operative tachycardia was identified but no significant vaginal bleeding was recorded. The patient developed severe ‘air hunger’ and became incoherent approximately two hours post operatively. An emergency laparotomy revealed a posterior uterine wall laceration not appreciated at time of Caesarean section with massive intra-abdominal bleeding. Hysterectomy was undertaken. Total estimated blood loss (EBL) was 3500cc. The patient developed disseminated intravascular coagulation (DIC), acute renal failure and acute respiratory distress syndrome (ARDS). She was later determined to have severe cerebral anoxic injury and life support was withdrawn.

**Discussion Points**

Documentation of vital signs and timely communication of abnormal findings are critical to timely response. Alerting signs include tachycardia despite absence of pain. Blood pressures considered ‘normal’ may not be recognized as being significantly lower than pre-delivery if there is a history of gestational hypertension.

The CMACE review urged units to develop standardized scoring systems to help identify early obstetrical hemorrhage. Regular education and drill training for all staff is essential for any centre routinely involved in labour and delivery. Although not discussed in this particular patient’s chart, the role of obesity in surgical access, visualization and time interval between ‘incision to decision’ cannot be ignored. Obesity is also an established risk factor for labour dystocia and need for emergency Caesarean delivery. As rates of obesity are increasing exponentially, obstetrical care providers must establish standardized and specialized care plans for pregnancy in the obese population.
Obstetric Hemorrhage - Case 2
In some cases, routine identification of risk and early management are unable to avert maternal death.
A woman in her forties, G10 P9 was induced for suspected post dates status and fetal macrosomia. She had limited prenatal care but reported nine prior term vaginal deliveries without complication. She had appropriate BMI and no history of significant bleeding outside of pregnancy. Following an uncomplicated labour, she had a spontaneous vaginal delivery of a 2.9 kg infant. She underwent active management of the third stage of labour, receiving 5 units oxytocin IV. The perineum was intact. At approximately two hours post delivery, the in-house Obstetrics resident was called to assess for increased bleeding.

The patient was hemodynamically stable with an estimated blood loss (EBL) of 500cc, expressed with bimanual massage. She received 250 ug of carboprost intramuscularly and an indwelling catheter was placed in the bladder. A CBC and coagulation screen was ordered. Thirty minutes following, the patient continued to have on-going bleeding with an EBL of 2000 cc. A repeat dose of carboprost was given and the patient was taken to the OR for surgical management. Emergency laparotomy revealed an atonic uterus. The patient received eight units of packed red blood cells and fresh frozen plasma, and a decision was made for urgent subtotal hysterectomy.

Despite surgical hemostasis, the patient proceeded to ‘crash’, and ICU attendance was requested. The patient had a cardiac arrest and a full code was called. Despite extensive efforts, the patient could not be resuscitated.

Discussion Points
Appropriate management was undertaken in this case; however, the following could have been considered:

- More frequent and extensive use of uterotonic agents
- Trial of uterine compression balloon while preparing for laparotomy
- More aggressive use of blood products. Obstetricians and anesthesiologist are encouraged to learn from the trauma literature regarding massive transfusion protocols, which include earlier platelet infusion, recombinant factor V11, and other appropriate therapeutic management.
Amniotic Fluid Embolism

Amniotic fluid embolism (AFE) is a rare and catastrophic event occurring at or around the time of delivery. It is believed to occur when amniotic fluid enters the maternal circulation and leads to cardiogenic shock, respiratory failure, and a systematic inflammatory response similar to anaphylaxis.

There were four deaths due to amniotic fluid emboli and one from air embolism in Alberta from 1998-2011. All but one patient was over 25 years of age and two patients were over 35 years. Four of the five patients were multiparous and were delivered by Caesarean section (primary Cesarean =3). In all patients, the onset of symptoms occurred at or following delivery and the interval between collapse and death was short.

**AFE - Case 1**
A woman between 35-40 years of age, G3P1 presented at term with spontaneous rupture of membranes. Her prenatal course was uncomplicated. Oxytocin was used for induction and an epidural was inserted. As labour progressed, there were two episodes of fetal bradycardia associated with maternal dyspnea at which time the patient became unresponsive and required supplemental oxygen. A diagnosis of either pulmonary emboli or amniotic fluid emboli was considered and an emergent Caesarean section recommended. A healthy female infant was delivered within an appropriate time. Oozing from the uterine incision was controlled with over-sewing prior to abdominal closure. In the recovery room, heavy vaginal bleeding was soon apparent; ICU was contacted and the patient was returned to the OR for laparotomy and hysterectomy. Heroic measures to control bleeding followed and despite aggressive and appropriate resuscitation manoeuvres that included massive blood products transfusion and administration of recombinant factor Vlla, the patient was pronounced dead. Autopsy confirmed an amniotic fluid emboli with numerous fetal squamous cells present within the maternal pulmonary vessels.

**Discussion Points**
This case illustrates the high mortality rate (approximately 20%) associated with amniotic fluid embolism even in optimal circumstances [4].

**AFE - Case 2**
An immigrant women between 35-40 years of age, G4P3 (SB1) was admitted at 41 weeks gestation for induction of labour with oxytocin. The indications for induction were postdates status and prior stillbirth. Labour progressed and fetal well-being was considered reassuring until transition to the second stage of labour. At this time, there was acute onset of fetal heart rate decelerations, coinciding with an altered level of maternal consciousness. Delivery was therefore expedited which resulted in a satisfactory neonatal outcome. However, the maternal condition continued to deteriorate with the patient remaining unresponsive, dazed and dyspeic. With high volume supplemental oxygen, reduced O₂ saturations were recorded. A brisk post partum hemorrhage soon followed delivery of the placenta. Appropriate medical and surgical interventions for postpartum hemorrhage were delayed for several hours. A ‘Code Blue’ was called and a second obstetrician arrived and commenced...
aggressive resuscitation measures. An immediate hysterectomy was performed. However, overwhelming maternal hypovolemia and coagulopathy could not be corrected and an intraoperative death was called.

**Discussion Points**

There were significant communications issues that compromised the patient’s care that led to her ultimate death. The patient’s clinical presentation was consistent with an AFE but this was not recognized by the attending staff. Ongoing postpartum hemorrhage contributed to the acute onset of anaemia and fulminating disseminating intravascular coagulation (DIC). These events unfolded in an environment in which a team of specialized obstetricians and anaesthetists were “in house” and minutes away but were not contacted until the patient’s status was critical.

AFE is a rare but serious complication of pregnancy with a reported incidence of 2.0 - 6.1 cases per 100,000 [1,3]. It has often been suggested that the prognosis is invariably fatal, but data from national databases suggest a realistic case fatality rate of 20% [4]. The first case illustrates that even with optimal care, (including a prompt diagnosis and treatment of PPH and DIC) the degree of hemorrhage and coagulopathy may continue to have devastating consequences. Both patients had risk factors for this rare complication: increased trending to advanced maternal age, ethnic minority women, and induction of labour and operative vaginal or Cesarean section deliveries. Other characteristics include multiple pregnancies, obesity and co-existing medical problems. Both case studies illustrate that symptoms are apparent shortly before or soon after delivery.

The clinical features of AFE include - sudden onset of fetal compromise (where applicable) associated with one or more of the following maternal features: premonitory symptoms or altered levels of consciousness, dyspnea, hemorrhage, hypotension and coagulopathy. Subsequent cardiac dysrhythmia and arrest and seizures may adversely influence the maternal resuscitation. In view of the severity and the nature of symptoms, and the absence of prompt delivery, the perinatal mortality rate may be high. The risk factors noted above together with the clinical findings permit a clinical diagnosis. A team approach to supportive therapy may optimize the maternal outcome. With appropriate care, case survival rates in the order of 80% may be achieved. In the presence of coagulopathy the use of recombinant factor VIIa has been proposed. In a report by Knight et al., 14 women were treated with recombinant factor VIIa for coagulopathy and 13 survived [4]. Failure to control the general bleeding with a conservative approach should prompt timely surgical intervention before the onset of DIC. Thus, similar to obstetrical hemorrhage, patients with suspected AFE should be treated with an aggressive, early and multi-disciplinary management approach.
Shared Learning - prevention of maternal deaths from obstetrical hemorrhage and amniotic fluid embolism

- Patients should undergo prenatal care with regular review and recognition of risk factors for postpartum hemorrhage, including multiparity and obesity.

- Ongoing practice-drills for management of the hemorrhaging and unstable patient and continuing medical education should be mandatory for all staff involved in care of obstetrical patients.

- Systematic, detailed and frequent recording of vital signs postpartum with recognition and action to abnormal findings, including early notification and attendance by the responsible physician, should be established in all centres involved in obstetrical care. Nurses should be given autonomy and guidance in cases where appropriate and timely action by attending physicians does not occur.

- All care-givers should be aware and trained in aggressive management of postpartum hemorrhage according to established protocols including use of uterotonics, compression balloons and massive transfusion protocols.

- Facilities providing obstetrical services and obstetrical units should regularly review protocols and guidelines for emergency management of unstable patients. Quality assurance should be approached by a multi-disciplinary group that includes obstetrical care providers (obstetricians, family physicians and registered midwives), nurses, anesthesiologists, blood bank, etc.

- Consider ectopic pregnancy as a differential diagnosis in women of reproductive age presenting with clinical signs & symptoms that mimic an ectopic pregnancy, confirmation should include:
  - measurement of the serum beta human chorionic gonadotropin (beta hCG)
  - Prompt ultrasound evaluation (transvaginal)
  - Prompt medical and surgical consultation.
References


PRE-ECLAMPSIA & ECLAMPSIA
AS CAUSES OF MATERNAL MORTALITY IN ALBERTA

Kara Nerenberg, MD, MSc, FRCPC

Preeclampsia/eclampsia, a hypertensive disorder of pregnancy, is a common pregnancy-related disorder that is associated with serious perinatal and maternal morbidity and mortality worldwide [1]. As outlined in the Society of Obstetricians and Gynaecologists of Canada (SOGC), guideline Diagnosis, evaluation and management of the hypertensive disorder of pregnancy (2014), preeclampsia typically is defined as hypertension (HTN) in pregnancy (diastolic blood pressure ≥ 90) AND urinary protein of ≥ 300 mg in 24 hours after 20 weeks gestation [2]. However atypical forms of preeclampsia (without proteinuria or hypertension) frequently occur in up to 30% of women [2,3]. Preeclampsia represents a spectrum of disease severity from non-severe to severe forms (see Sibai, 2006 Appendix 1 for criteria for severe preeclampsia) [1]. Eclampsia, a seizure in the setting of preeclampsia, represents one form of severe preeclampsia [4]. In general, women with more severe forms of preeclampsia have higher rates of adverse clinical and obstetrical outcomes[1].

While it is well known that underdeveloped countries have high maternal mortality rates due to preeclampsia (15-20% of all maternal deaths), preeclampsia is often overlooked as a cause of maternal death in developed countries [1]. Importantly, both the UK Confidential Enquiry into Maternal Deaths and the US Pregnancy Mortality Surveillance System identified preeclampsia as one of the top three causes of maternal mortality [5]. In the UK, preeclampsia was the second leading cause of maternal deaths at 14.8% (0.83 per 100,000 pregnancies) and in the US third at 16% [5,6]. Time trends in the US from 1991 to 1999 demonstrated a slight decrease in the percentage of maternal deaths due to preeclampsia which is thought to be due to improved medical and obstetrical care of women with preeclampsia [6]. Alarmingly, in the UK there is an actual increase in the number of direct maternal deaths due to preeclampsia from 2003 to 2008 [5].

The underlying mechanism of death in women with preeclampsia generally centers around high systolic blood pressure (SBP) [1]. High SBP, especially levels > 150-160 mmHg, directly causes several maternal complications, such as intracranial hemorrhage, seizure, pulmonary edema, liver rupture and multi-organ system failure and ultimately maternal death [1,5]. In the UK Confidential Enquiries into Maternal Deaths report, of the 22 women who died of hypertension-related causes, nine were directly related to intracranial hemorrhage in the setting of severe systolic hypertension [5]. In addition, five deaths were related to eclampsia with seizure causing cardiac arrest and ultimately anoxic brain injury [5].

Numerous professional organizations consider preeclampsia as a largely preventable or avoidable cause of maternal death for two main reasons [2,5,7]. First, effective antihypertensive medications exist (in both intravenous and oral preparations) to ensure that maternal systolic blood pressure (SBP) remains less than 150 mmHg in order to prevent maternal intracranial
hemorrhage. As a result, the UK Confidential Enquiry and the UK’s National Institute for Health and Clinical Excellent (NICE) guidelines recommend that “All pregnant women with preeclampsia and a systolic blood pressure of 150-160 mmHg or more require urgent and effective anti-hypertensive treatment”[5,7].

They also recommend that the SBP be less than 150 mmHg within two hours initiating acute antihypertensive treatment [5,7]. This simple, easily implementable intervention strategy that can save many maternal lives has become one of the “top ten lessons” to clinicians from the UK Confidential Enquiries report.

Second, in addition to antihypertensive medications, numerous other evidence-based medical and obstetrical therapies already exist in everyday clinical practice settings to treat women with preeclampsia that can also prevent maternal morbidity and mortality[1,8]. Despite the availability of these therapies, the UK Confidential Enquiry report, found that in 20 of the 22 women who died of preeclampsia related complications, these simple, widely-available therapies are not consistently used [5]. They termed these deficiencies “substandard medical care” and grouped them as predominantly relating to: ineffective or inadequate treatment with antihypertensives; inadequate referral to specialist care (obstetrician or maternal-fetal-medicine [MFM] specialists); inappropriate recognition of the severity of preeclampsia, especially epigastric pain as HELLP syndrome (Hemolysis, Elevated Liver Enzymes and Low Platelets; part of the preeclampsia severe spectrum); and lack of (or late) use of magnesium sulphate for eclampsia prophylaxis, in which the seizure directly led to the maternal death [5].

Objectives:
The Maternal Mortality Working Group presents a critical review of two cases of maternal mortality directly caused by preeclampsia as a means of highlighting key modifiable components in the future care of women with preeclampsia. The overall goal is to prevent further maternal mortality from preeclampsia in Alberta.

**Preeclampsia/ Eclampsia - Case 1**
An obese woman between 20-25 years of age, G1 was diagnosed with “gestational hypertension”, at 33 weeks’ gestation and was treated at home with Labetalol 100 mg po bid. In retrospect, at the time, the patient actually met the criteria for preeclampsia at 33 weeks (blood pressure 144/96 with 0.5 grams of proteinuria). The patient’s blood pressure remained high at home up to 152/110 and for three weeks she experienced progressive shortness of breath and chest pains. She was subsequently admitted to a level I hospital at 37 weeks with shortness of breath and cough. She had clinical and radiologic evidence of severe pulmonary edema. She was immediately transported to a level III hospital but had a cardiac arrest (PEA) en route. At the level III hospital, despite emergency Caesarean section, treatment with magnesium sulfate and antihypertensives, and involvement of a multidisciplinary team of specialists (intensive care, obstetrics, MFM, obstetrical medicine, and neurology) the patient died. Autopsy confirmed that the patient’s death was directly caused by the sequelae of preeclampsia.
Discussion Points

1. **Prompt recognition of preeclampsia:** Women with hypertension in pregnancy need to be repeatedly evaluated for preeclampsia by accurately assessing for the presence of proteinuria with either a spot protein to creatinine ratio or a 24 hour urinalysis, as well as for other biochemical abnormalities [2]. In addition, women should be counselled about the common symptoms of preeclampsia and when to seek medical attention [7].

2. **Early referral to specialist care:** Once preeclampsia is identified, referral to specialized obstetrical care (MFM or High-risk Obstetrics) is recommended [5].

3. **Surveillance for the development of any acute indications for delivery:** Once preeclampsia is identified, obstetrical management is generally provided in an in-patient setting or established antenatal home-care program in order to monitor for the development of maternal indications (e.g., pulmonary edema, cerebral edema, HELLP syndrome, etc.) or fetal indications (e.g., intrauterine growth restriction, abnormal dopplers, etc.) for urgent delivery [2,7].

4. **Adequacy of treatment of hypertension:** The goal for treatment is to obtain a blood pressure of <155/105 mmHg (SOGC 2014) [2] or <150/100 (NICE 2010) [7] through the use of either intravenous or oral antihypertensive medications that are considered safe in pregnancy. In women with either preeclampsia or gestational hypertension, blood pressure must be closely monitored to ensure that BP actually meets treatment targets [7]. In addition, in obese hypertensive pregnant women, higher doses of commonly used antihypertensive medications are commonly required. An appropriate size BP cuff should be used for the measurement of BP.

5. **Symptoms of shortness of breath in pregnant women need to be thoroughly investigated:** It is important that shortness of breath be investigated in pregnancy in order to determine etiology (e.g., pulmonary embolism, pulmonary edema, and peripartum cardiomyopathy, etc.). Dyspnea of pregnancy should remain a diagnosis of exclusion [5]. In women with preeclampsia, a chest x-ray is generally performed to exclude pulmonary edema.

6. **Recognition of women at increased risk of preeclampsia early in pregnancy:** Women with several risk factors for preeclampsia may require closer surveillance for the development of preeclampsia. For example, this patient had several well-known preeclampsia risk factors including: first pregnancy, obesity, and probable chronic hypertension as evidenced by early antenatal records. In addition, in high-risk women, guidelines suggest the implementation of measures to prevent preeclampsia (e.g., use of aspirin 81 mg daily before 16 weeks gestation and calcium supplementation)[2,7].

7. **Clear documentation of the patient’s antenatal course:** Documentation of all components of routine antenatal visits is essential to facilitate identification of clinical issues as they arise (e.g., hypertension and proteinuria)[5].
**Preeclampsia/ Eclampsia - Case 2**

A woman in her thirties, G2P0A1, developed gestational hypertension with significant peripheral edema at approximately 34 weeks’ gestation. A screening urine dipstick was negative but no other urinalyses were sent to the lab for measured protein level. The patient was followed as an outpatient by high-risk obstetrics as well as antenatal homecare. At 35 weeks, fetal ultrasound showed an estimated fetal weight at 5-10th percentile, but no other features of placental insufficiency. Of note, there was no documented spot protein to creatinine ratios, 24 hour urine protein measurements or other preeclampsia labs performed from 34-37 weeks. At 37 weeks, the patient was admitted for an induction of labour. Blood pressure at admission was 166/96 (140/90 the day prior) with documented proteinuria. Approximately 18 hours later, the patient developed epigastric pain and hyperreflexia, at which time magnesium sulfate infusion was initiated. Shortly thereafter, the patient had an eclamptic seizure followed by a cardiac arrest requiring resuscitation. An emergency Caesarean section was performed. CT head showed an intracerebral hemorrhage. Despite neurosurgery and aggressive medical treatment in the intensive care unit, the patient died. On autopsy, the cause of death was determined to be an intracerebral hemorrhage secondary to preeclampsia.

**Discussion Points**

1. **Awareness that 25-50% of women with gestational hypertension will progress to preeclampsia:** Given the high rate of progression to preeclampsia in this population, close clinical surveillance of women with gestational hypertension is required [3]. Part of this surveillance may involve laboratory testing for preeclampsia [7].

2. **Recognition of atypical forms of preeclampsia / eclampsia:** These conditions are often difficult to diagnose, as many women do not have the main components of preeclampsia (i.e., neither hypertension nor proteinuria). Importantly, proteinuria is absent in up to 30% of women with preeclampsia and in 14% of women with eclampsia [3,10]. In addition, in other atypical forms of preeclampsia, women may have a relatively normal blood pressure. As such, clinicians need to consider broader range criteria beyond simply hypertension and proteinuria to diagnose preeclampsia (e.g., cerebral symptoms, fetal growth restriction, other laboratory abnormalities, etc.)[3].

3. **Warning signs of eclampsia:** Up to 75% of women with eclampsia have at least one warning symptom including: headache, visual changes, or epigastric discomfort [9]. Women may also have other findings on clinical exam, including hyperreflexia and clonus. However, the absence of these findings does not reliably ensure a woman will not develop eclampsia. As such, a low threshold for the initiation of magnesium sulfate should be considered in any woman with preeclampsia and gestational hypertension [3,7].
4. **Early initiation and regular use of magnesium sulfate for the prevention of eclampsia in women with preeclampsia**: The MAGPIE trial, a large, international randomized controlled trial, demonstrated that the use of magnesium sulfate was associated with a 58% reduction (95% confidence interval 40-71%) in the rate of eclampsia in women with preeclampsia [8]. As preeclampsia can progress very quickly to severe forms of preeclampsia and eclampsia, magnesium sulphate ought to be initiated early in the delivery of women with suspected preeclampsia [7].

5. **Control of blood pressure in the setting of preeclampsia to prevent intracerebral hemorrhage (ICH)**: As outlined above, based upon the risk of ICH with severe maternal HTN, guidelines recommend aggressive treatment of severe HTN to < 150-155/100-105 [2,7].

6. **Timing of delivery**: The decision regarding the timing of delivery is generally complex and multifactorial. Evidence suggests, that after 37 weeks’ gestation, there were no maternal or fetal benefits associated with expectant management, therefore delivery is generally recommended at or beyond this gestational age [10]. Prior to 37 weeks' decisions regarding the timing of delivery need to consider a combination of features related to the status of the mother and fetus.

**Conclusions:**
In summary, preeclampsia is a common pregnancy related disorder associated with high maternal morbidity and mortality, which are largely preventable through the early implementation of widely available, evidence-based medical and obstetrical therapies. With the increasing incidence of preeclampsia in the province of Alberta [11], it is important for clinicians involved in the care of pregnant women to review the following shared learning in providing care for women at risk for preeclampsia.

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**Shared Learning - prevention of maternal deaths from preeclampsia**

- Identify women at risk of preeclampsia in order to implement appropriate preventative and screening strategies.

- Once preeclampsia is recognized, pregnant women need to be urgently referred for specialist care (obstetrics and MFM in conjunction with internal medicine specialists).

- Close monitoring for the development of features of severe preeclampsia.

- Blood pressure should be effectively treated to <150-155/100-105, magnesium sulfate initiated early, and decisions regarding delivery based upon maternal and fetal indications.
References


**MATERNAL SEPSIS**

Stephanie Cooper MD, FRCSC & Eliana Castillo MD FRCPC

**Sepsis** refers to the systemic inflammatory response syndrome (SIRS) secondary to infection [1]. The term ‘septic shock’ is used in the setting of severe sepsis associated with tissue hypoxia and cellular damage leading to multiple organ system dysfunction and hypoperfusion [1]. The contribution of sepsis as a cause of maternal mortality has been estimated between 2.7% in developed countries and 11.6% in developing countries [2]. The UK Confidential Enquiry from 2008-2010 identified sepsis as the leading cause of direct maternal death [3] and pointed out that delayed diagnosis and therapy were common denominators across cases.

Traditionally, and for the purposes of this review, maternal deaths from genital tract infection or sepsis directly related to delivery but not involving the genital tract (i.e. spinal abscess following regional anesthetic) have been classified as direct maternal deaths. Other infections unrelated to the genital tract but for which pregnant and postpartum women are known to be at increased risk of morbidity and mortality like influenza [4-7], or whose effects might be amplified by the physiological adaptations to pregnancy like invasive pneumococcal infections (i.e. pneumococcal meningitis and pneumonia) [8,9] are classified as indirect maternal deaths. Maternal deaths from overwhelming sepsis where the pregnancy is considered as having nothing to do with the infection are classified as coincidental deaths.

Risk factors for sepsis in the obstetric population include existing infection such as chorioamnionitis, pyelonephritis and pneumonia. Additional risk factors include preterm birth, Caesarean birth, primiparity and obesity [10]. Trends seen in maternity care such as increasing rates of obesity, advanced maternal age, Type 2 diabetes and multiple births from assisted reproductive technologies increase the likelihood of many of these scenarios. Delayed recognition of sepsis occurring during pregnancy is not surprising, given that sepsis “warning signs” such as increased heart or respiratory rate, widely used among the adult non-obstetric population to define SIRS/sepsis [1], are inherently associated with normal pregnancy and labour. Findings may be further confounded by the effects of medications such as prostaglandins, magnesium sulphate and regional anaesthetic on maternal signs and symptoms of infection. Of further concerns is that the pregnant woman may be more vulnerable to complications of sepsis due to underlying physiologic changes, resulting in pulmonary edema, disseminated intravascular coagulation (DIC) and microvascular thrombosis [3].

Presenting symptoms and signs of sepsis can be variable and differ from the non-pregnant state. Changes in maternal physiology influence vital signs and laboratory investigations and may affect the ability to accurately diagnosis sepsis in pregnancy. Diagnosis of sepsis in the intrapartum period is even more complicated due to further changes in heart rate, respiratory rate and the experience of pain.
One Alberta resident and one out-of-province woman were classified as direct maternal deaths attributed to sepsis during the review period. Sepsis also accounted for five indirect maternal deaths and four coincidental deaths in Alberta during the review period. No other infections (e.g. AIDS) accounted for maternal deaths in Alberta during the review period.

**SEPSIS - Direct Maternal Deaths**

The two direct maternal deaths due to overwhelming sepsis both occurred following rupture of membranes and chorioamnionitis. Chorioamnionitis is an acute inflammation of the membranes and chorion of the placenta, typically due to ascending polymicrobial infection in the setting of ruptured membranes. Risk factors include prematurity, long duration of membrane rupture, long duration of labour, multiple vaginal examinations in labour, history of colonization with Group B Streptococcus, sexually transmitted infections and bacterial vaginosis [10]. In this inquiry, one case was preterm and the other term, but neither patient reported prolonged history of leaking fluid vaginally on presentation. Both patients presented with clinical signs and symptoms concerning for early chorioamnionitis which later progressed to sepsis. Although recognition and management was felt to be appropriate, early recognition and aggressive management remain paramount to prevention of adverse maternal outcomes and should be highlighted.

A critical review of two cases of maternal mortality related to sepsis is presented as a means of highlighting key modifiable components in the future care of women with infections during pregnancy.
Maternal Sepsis - Case 1
A woman in her twenties, G1P0, with a history of substance abuse and late initiation of prenatal care, presented at 38 weeks gestation with unremitting abdominal pain. She reported vaginal fluid leaking throughout the day and decreased fetal movement. Fetal tachycardia (baseline 170-180) with variable decelerations but good variability was identified. Sterile speculum exam confirmed rupture of membranes and the cervix was noted to be 1 cm dilated but 'thick'. Maternal pulse was 115 bpm, temperature was 36.9 C and blood pressure was 128/66. Chorioamnionitis was suspected but differential diagnosis included placental abruption; especially as a history of cocaine use was considered (the toxicology report was later negative for cocaine). Cefoxitin 2 grams IV q 6 hours was ordered.

Maternal white blood count was found to be 30.6 with a left shift, hemoglobin was 167 and platelets were 162. Within 2-3 hours, the cervix had progressed to 5 cm dilation but a stat caesarean section was called due to progressive fetal heart rate decelerations. The patient received a general anesthetic and vitals were stable throughout the procedure although there was no further temperature recorded in the patient’s records other than her initial reading at presentation. Thin meconium and foul smelling liquor was noted at the time of the delivery and the neonate was transferred to NICU, but later succumbed to overwhelming sepsis. Maternal blood loss was not noted to be excessive (estimated loss of 400cc) although due to a ‘boggy uterus’ the patient received a dose of ergotamine.

In the recovery room, the patient’s temperature was 37.5, BP was 105/54 and HR was 182. Peripheral pulses were ‘not present for minutes’ and BP dropped to 60s/40s. The infectious diseases service was consulted and metronidazole was ordered following IV crystalloid infusion (5L). Maternal skin was noted to be mottled and erythematous.

Laboratory results in the recovery room revealed unchanged hemoglobin at 164, but thrombocytopenia was indentified with a platelet count of 29 and a white cell count of 60.3. The intensive care unit was consulted for transfer. The infectious disease service recommended cefotaxime 2 grams IV q 8 hours and metronidazole 500 mg IV q 12 hours.

Upon transfer to the ICU, the patient deteriorated over the next six hours. Laboratory results showed DIC and despite administration of inotropes and IV steroids, the patient remained unstable. The ICU team then recommended a hysterectomy to remove the source of infection. However, intra-operatively and prior to completion of the hysterectomy, the patient suffered a cardiac arrest and could not be resuscitated despite aggressive measures.
Discussion Points

The circumstances in this particular case emphasises the dramatic and aggressive course that chorioamnionitis may take. Despite a normal temperature upon presentation, the patient showed other concerning signs of chorioamnionitis and intravenous antibiotics were given as indicated. The typical antimicrobial regime recommended for chorioamnionitis is ampicillin and gentamycin with consideration of anaerobic coverage using clindamycin or metronidazole, especially in the case of Caesarean delivery. Evidence comparing regimes is limited, and use of cefoxitin as in this case is considered an appropriate alternative.

Although a more expeditious decision for Cesarean section may be queried in hindsight, there is no evidence that this would have changed the course for either the mother or the baby.

The recommendation for laparotomy given the degree of patient instability may be in question. Although surgical removal of an infected source is indicated for sepsis, this patient did not have an abscess and the ‘source’ of the infection had been removed with delivery. Although, the patient’s death was likely not impacted by the second surgery, treatment in the early postpartum period for chorioamnionitis is medical support as a major surgery may only contribute to morbidity.

Maternal Sepsis - Case 2

A woman in her late twenties, G1P0, at 29 weeks gestation was transferred from a rural setting to a tertiary site by air ambulance following confirmed rupture of membranes for one day. The patient had a history of bacterial vaginosis in the pregnancy but no other risk factors were noted for premature rupture of membranes or chorioamnionitis. Maternal temperature was 37.9 C and vaginal discharge was described as mucopurulent. Fetal heart rate was 160 with good variability but with three decelerations. As the patient was contracting, she received tocolysis in the form of Indomethacin 100 mg rectal suppository and magnesium sulphate infusion of 2 grams per hour following a 4 gram IV bolus. She further received 12mg of dexamethasone IM, ampicillin 2 grams IV and erythromycin 1 gram IV. During the patient’s air transfer she became progressively more hypotensive, which was treated with IV fluids, reduction of magnesium infusion rate and calcium gluconate as a magnesium antidote. The maternal heart rate was 97-100 bpm. Upon arrival at the receiving hospital, the fetal heart tracing showed normal baseline and variability and maternal vital signs had stabilized. The WBC was 26.8 with a left shift. The magnesium infusion was maintained as was the ampicillin and erythromycin. Expectant management was chosen as it was felt there was no evidence of chorioamnionitis. Perinatology was consulted and a fetal ultrasound performed which showed fetal ascites and liver calcifications. Fetal assessment was otherwise reassuring. Later that day, the fetal heart tracing became abnormal and a decision was made for emergency caesarean section. This procedure was considered uncomplicated. The baby was transferred to the NICU where it later died of presumed sepsis at 3 hours of age. The patient received clindamycin and gentamycin post operatively.

In the initial hours following delivery, the patient was stable and afebrile. However, she
later developed tachycardia, shortness of breath and nausea. Blood work showed worsening leukocytosis and evidence of DIC. She was noted to have a mottled appearance. The patient was transferred to the ICU where she became apneic and a cardiac arrest soon occurred. Despite aggressive resuscitation, the patient died.

Blood cultures were negative for both mother and baby, but the patient had already received antibiotics by the time of their draw. Autopsy confirmed sepsis from ascending intrauterine infection as cause of death.

Discussion Points

Management of this case illustrates the insidious onset that sepsis may take. However, the decision for expectant management was based on an assessment that there were no signs or symptoms of chorioamnionitis. Although pyrexia (temperature >38 degrees C) is common and perhaps the most specific sign of chorioamnionitis, a normal temperature does not exclude infection. This patient presented with a temperature of 37.9, which although not meeting criteria for pyrexia, is considered higher than expected and concerning given her clinical presentation.

The antibiotic protocol given to the patient was based on the ORACLE trial, with the main goal being to increase latency and improve neonatal outcomes. Given the clinical presentation, the broad-spectrum antibiotics for chorioamnionitis could have been a more appropriate choice.

The use of tocolytics in suspected chorioamnionitis is generally considered contraindicated. However, given that the patient was remote from term and air ambulance transfer was required, use may be considered justified for transfer duration only. However, IV magnesium sulphate infusion is not considered an appropriate choice for multiple reasons; evidence does not support its efficacy as a tocolytic, IV infusions may be associated with toxicity and therefore require close monitoring and the side effects of the drug may mimic or mask those of sepsis. The fetal ultrasound findings of ascites and liver calcifications were not explained by the maternal presentation and post-mortem findings of the neonate were unavailable.

Chorioamnionitis usually results in a good outcome for both mother and baby, but our review illustrates two tragic cases of young, previously healthy women and their babies who rapidly succumbed to sepsis secondary to ascending uterine infection following rupture of membranes.

Shared Learning - prevention of maternal deaths from chorioamnionitis

- Awareness of risk and potential outcomes of chorioamnionitis.
- Early recognition and aggressive use of appropriate broad-spectrum antibiotics are considered paramount to the prevention of maternal sepsis and its complications from chorioamnionitis.
SEPSIS - *Indirect and Coincidental Maternal Deaths*

Five maternal deaths were classified as indirect maternal deaths: four antepartum (second and third trimester only) and one postpartum (<42 days). Three women died from respiratory tract-related sepsis (one confirmed case of H1N1-related sepsis, one sepsis with undetermined origin), one from pyelonephritis and one from pneumococcal meningitis. Four deaths after 42 days from conclusion of pregnancy were related to sepsis. Refer to the table below. Obesity and mental health/substance abuse were recurrent themes in the cases reviewed. Failure to recognize some of these women were septic on initial presentation may have contributed to their deaths.

<table>
<thead>
<tr>
<th>Type of death</th>
<th>Timing (AP/&lt;42/&gt;42)</th>
<th>Comorbidities</th>
<th>BMI</th>
<th>Organism or Clinical syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>INDIRECT Antepartum 28w GA</td>
<td>none</td>
<td>N/A</td>
<td>Severe sepsis undetermined origin</td>
</tr>
<tr>
<td>2</td>
<td>INDIRECT Antepartum 17w GA</td>
<td>asthma, morbid obesity</td>
<td>45</td>
<td>H1N1 Severe sepsis</td>
</tr>
<tr>
<td>3</td>
<td>INDIRECT Antepartum 21w GA</td>
<td>substance abuse, brain injury</td>
<td>N/A</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>3</td>
<td>INDIRECT Postpartum &lt;42 days</td>
<td>severe anemia, obesity</td>
<td>32</td>
<td>Pyelonephritis</td>
</tr>
<tr>
<td>5</td>
<td>INDIRECT Antepartum 21w GA</td>
<td>alcohol abuse, overweight</td>
<td>25</td>
<td>Pneumococcus Meningitis</td>
</tr>
<tr>
<td>6</td>
<td>Coincidental Postpartum 11 mo</td>
<td>SLE</td>
<td>N/A</td>
<td>Group A Strep Sinusitis</td>
</tr>
<tr>
<td>7</td>
<td>Coincidental Postpartum 10 mo</td>
<td>obesity</td>
<td>40</td>
<td>MRSA Necrotizing Pneumonia</td>
</tr>
<tr>
<td>8</td>
<td>Coincidental Postpartum 10 mo</td>
<td>substance abuse</td>
<td>N/A</td>
<td>Septic shock</td>
</tr>
<tr>
<td>9</td>
<td>Coincidental Postpartum 10 mo</td>
<td>asthma, depression, substance abuse</td>
<td>N/A</td>
<td>Influenza A MRSA super-infection Pneumonia</td>
</tr>
</tbody>
</table>
**Indirect Death from Sepsis - Case 1**

A woman in her late twenties, G1, without any comorbidities sought medical attention through ER at a Level 2 hospital at 28 weeks’ gestation. She complained of decreased fetal movements and severe, new onset cough that would make her vomit; she was reassured and sent home. She presented again a week later, with severe back pain, feeling unwell, and was given a diagnosis of sciatica, treated with analgesics and sent home. Twenty-four hours later she presented again for severe dyspnea: she was febrile and hypoxemic; she was admitted to ICU, broad-spectrum antibiotics and Tamiflu were started. She continued to deteriorate, became progressively acidic and hypoxic. She had a cardiac arrest prior to being transferred. Resuscitation efforts were not successful. Autopsy cause of death was sepsis due to an undetermined origin.

**Indirect Death from Sepsis - Case 2**

A woman in her twenties, G1, morbidly obese (BMI 45), with past medical history of moderate persistent asthma and depression. Presented to obstetric care provider office at 15 weeks for possible allergic reaction to clindamycin (rash); noted to have URTI symptoms. A week later presented to ER with severe cough and dyspnea not relieved by inhalers (short and long acting beta agonists and inhaled corticosteroid); she was sent home on oral antibiotics as there was a small right upper lobe consolidation on chest x-ray. Twenty-four hours later she presented to ER again with worsening dyspnea, fever, cough and new diarrhea; she was hypotensive and tachycardic. She was sent home after IV fluids and analgesics were given. She presented again, within 72 hours of first ER visit with hypoxemic respiratory failure: admitted to ICU at a Level 3 hospital, but transferred within 48 hours to receive ECMO given severe hypoxia and hemodynamic instability. Care was withdrawn after three weeks in the setting of multiple complications including intracranial hemorrhage. Influenza A (H1N1) was recovered from upper respiratory samples collected at time of ICU admission. A medical autopsy was not performed.

**Discussion Points**

1. Awareness regarding the increased risk of influenza-related morbidity and mortality posed by pregnancy: Both of these patients (and two others not presented) sought medical attention for respiratory symptoms during the flu season (on at least two occasions) prior to being recognized as having influenza-like illness, being offered testing or empiric treatment. The patient in case 1 didn’t have any comorbidity, emphasizing that influenza in pregnancy can be deadly regardless of comorbidities. Hospitalization rates for influenza are 5 times higher for pregnant women than age matched controls and up to 10 times higher if they have comorbidities [4, 5].
2. Influenza is a vaccine-preventable illness: Universal immunization for influenza during pregnancy is recommended by NACI/ACIP/ACOG/SOGC as despite suboptimal vaccine effectiveness, influenza immunization has been shown to decrease rates of maternal, fetal and neonatal morbidity arising from respiratory illnesses [12-14]. In Alberta in the 2011-2012 seasons, only 12% of pregnant women were immunized for influenza. There was no mention in the prenatal record of influenza immunization being offered to the two women discussed above; the other three women that died antepartum from sepsis, or the woman that died from Influenza A-sepsis in the post-partum period.

3. Diagnosis of sepsis in pregnancy is delayed usually until criteria for severe sepsis is met and management is guided by clinical impression and extrapolation of data derived from the adult non-obstetrical population: Evidence-based criteria of disease severity and outcome prediction models for sepsis in the obstetrical population are urgently needed. In one of two of the cases reviewed in this section, and one of the cases of chorioamnionitis women were “under-resuscitated” i.e. probably didn’t receive the amount of crystalloids a non-obstetric patient would receive under similar circumstances. This may reflect the clinicians fear to precipitate pulmonary edema to which the acutely-ill pregnant woman is at higher risk, but potentially at the expense of perpetuating hypoperfusion and ensuing multi-organ dysfunction.

4. There needs to be clear documentation on hospital records on key indicators like “time to antibiotics” or resuscitation goals: Once sepsis ensues and hypotension is detected survival decreases by 7.6% for each hour of delay in starting appropriate antibiotic therapy [15]. Timing of antibiotics could not be ascertained in any of the nine cases reviewed. This is a measurable quality indicator that could be used at any level and can help improve outcomes.

5. Case 2 was determined not to be a medical examiners case. A medical autopsy was not done. Physicians should request consent for medical autopsy for all maternal deaths. Importance of clinico-pathological review and standardization as it pertains to maternal mortality is critical in determining the cause of death. Best practices to improve the yield of clinico-pathological examinations include standardizing collection procedures for postmortem blood samples to minimize contamination [3] and obtaining a full set of histopathology samples, including bone marrow to assist in determining the presence and pattern of sepsis present [16].
References


Cardiac disease has become a leading cause of maternal mortality in developed countries of the world over the last 50 years. In countries with modern medical systems like Canada’s, cardiac disease has risen to near the top among causes of maternal death [1-4]. In the most recent maternal mortality reviews from the UK (1996-98) [1], maternal cardiac disease was not only the most common cause of indirect maternal death but the most common cause overall. In countries with less well developed medical systems and access to care, the leading causes of pregnant and postpartum women dying include bleeding, infection, preeclampsia/eclampsia and obstructed labour [5, 6]. In these countries maternal cardiac disease can also pose a significant risk, particularly among women with preexisting rheumatic heart disease and uncorrected congenital heart conditions.

Pregnancy-associated cardiac death is generally considered an INDIRECT cause of maternal death. Indirect maternal deaths are defined as “a death resulting from disease before or developing during pregnancy (not a direct effect of the pregnancy) which was obviously aggravated by the physiological effects of the pregnancy and caused the death.” Some maternal cardiac deaths, particularly those occurring late following an otherwise uneventful pregnancy, may be considered COINCIDENTAL, or “not related to the pregnancy, nor its complications or management.”

During the period of January 1, 1998 to December 31, 2011 there were 14 maternal deaths (during pregnancy or up to one year postpartum) due to cardiac/pulmonary vascular disease. Thirteen of the women were Albertans, and one was transferred from out-of-province but received her peripartum care and died in Alberta. Seven of the deaths occurred during pregnancy and seven occurred during the postpartum interval.
**Maternal Deaths during Pregnancy (n=7)**

There were three *antepartum maternal deaths due to myocarditis/ cardiomyopathy*. One of the deaths was due to acute idiopathic myocarditis resulting in congestive heart failure at 17 weeks gestation. Another woman developed chest pain and hypotension at eight weeks gestation and succumbed to myocarditis. The third antepartum death was a woman who collapsed with sudden cardiac death at approximately 35 weeks gestation and was found to have severe peripartum cardiomyopathy *(see Cardiac/Vascular - Case 1)*.

*Another maternal death was due to a spontaneous aortic dissection* resulting in hemopericardium and cardiac tamponade at 27 weeks gestation in a woman without prior cardiovascular disease or apparent underlying aortic abnormalities. The *fifth antepartum maternal death was a sudden unexplained death* during the third trimester in a woman subsequently found to have very small coronary arteries, presumed to be a sudden cardiac death.

Lastly, there were *two maternal antepartum deaths due to ruptured pulmonary arteriovenous malformations (AVM)*. One woman had known Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia) with pulmonary AVMs, and died at 18 weeks gestation following rupture of an AVM resulting in fatal massive hemothorax. The other woman had a prior history of empyema, and presented at 10 weeks gestation with hemoptysis and chest pain due to massive hemopneumothorax. She died despite a thoracotomy and prolonged resuscitation, and was found to have a ruptured pulmonary AVM on postmortem examination.

**Postpartum Maternal Deaths (n=7)**

The *seven postpartum maternal deaths were due to a variety of cardiac conditions*. One woman died of heart failure due to prosthetic aortic valve dysfunction resulting in decompensated congestive heart failure at four weeks postpartum, following an otherwise uneventful pregnancy *(see Cardiac/Vascular Case 2)*. Another woman developed acute aortic dissection in association with severe postpartum hypertension, leading to fatal hemopericardium *(see Cardiac/Vascular Case 3)*.

There were two postpartum maternal deaths due to myocardial infarction (MI): a woman with fatal MI due to spontaneous coronary artery dissection at 10 days postpartum, and a woman with fatal MI due to coronary artery disease at approximately three month postpartum.

There were two postpartum women who suffered sudden cardiac death: one woman experienced a sudden collapse at approximately three months postpartum and was found on autopsy to have right ventricular dysplasia, with a presumed cause of death of fatal postpartum dysrhythmia; another woman experienced an unexplained sudden cardiac death at five months postpartum.

Lastly, a young woman with preexisting myocardial disease (due to Tuberous Sclerosis) developed progressive heart failure during pregnancy. She survived a carefully planned delivery but then died approximately four months postpartum in the setting of superimposed sepsis, after being lost to medical follow-up *(see Cardiac/Vascular Case 4)*.
Cardiac Causes of Maternal Mortality

<table>
<thead>
<tr>
<th>Antepartum (n=7)</th>
<th>Postpartum (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cardiomyopathy/myocarditis x 2</td>
<td>• Aortic dissection due to severe HTN</td>
</tr>
<tr>
<td>• Peripartum cardiomyopathy (PPCM)</td>
<td>• Myocardial infarction x 2</td>
</tr>
<tr>
<td>• Aortic dissection</td>
<td>• CHF due to tissue valve failure</td>
</tr>
<tr>
<td>• Sudden Cardiac Death (small coronaries)</td>
<td>• Sudden cardiac death with RV dysplasia</td>
</tr>
<tr>
<td>• Ruptured pulmonary AVM x 2</td>
<td>• Sepsis in woman with severe pregnancy-associated decline in LV function</td>
</tr>
<tr>
<td></td>
<td>• Unexplained sudden cardiac death</td>
</tr>
</tbody>
</table>

Cardiac/Vascular - Case 1

A woman in her late thirties, G2P1, had one prior completed successful pregnancy. She was obese (BMI ~ 32) and a current smoker. At approximately 35 weeks gestation during her otherwise uneventful second pregnancy, while at home, she complained to her partner of feeling dizzy. She then collapsed to the floor and was found to be pulseless.

EMS arrived to find her in asystole and when she arrived in the ER a postmortem Cesarean section was performed (infant died) and the prolonged unsuccessful resuscitation (> 40 minutes) was called off. The postmortem exam revealed a dilated cardiomyopathy, consistent with dilated/peripartum cardiomyopathy (PPCM).

Discussion Points

Peripartum cardiomyopathy (PPCM) remains a leading cardiac cause of maternal mortality in Canada. Women may present with symptoms of congestive heart failure, thromboembolic phenomena, dysrhythmias or sudden cardiac death (as in this case). PPCM may present within the last month of pregnancy or up to five months postpartum. Because the symptoms of PPCM may overlap with normal pregnancy/puerperium, a high index of suspicion is required in order to make a prompt and accurate diagnosis and thereby minimize the risk of maternal morbidity and mortality.
**Cardiac/Vascular - Case 2**

A woman in her late thirties, G6, P5, had had a prior aortic valve replacement with a tissue valve performed nine years prior for aortic stenosis. During pregnancy she was on treatment with levothyroxine for hypothyroidism and paroxetine for depression. Her pregnancy was uneventful except for gestational diabetes requiring insulin and culminated in a successful elective repeat Cesarean delivery (and tubal ligation) near term. Peripartum she received prophylactic antibiotics and heparin and she was discharged home two days postpartum.

Two weeks postpartum she presented to her primary care physician with progressive dyspnea. Cardiomegaly and a possible infiltrate were seen on CXR, and furosemide, lisinopril and erythromycin were prescribed (but not taken). A week later she returned with increasing dyspnea and a productive cough, and a repeat CXR showed worsening bilateral congestion and/or pneumonia. She was admitted and treated with antibiotics for possible community acquired pneumonia, along with initiation of a beta-blocker due to tachycardia.

Transesophageal echocardiogram subsequently identified increased pulmonary pressures, left atrial dilation, moderate aortic, mitral and tricuspid regurgitation. She then suffered an in-hospital cardiac arrest with an unsuccessful resuscitation. Postmortem examination showed no pneumonia but confirmed cause of death as decompensated CHF due to stenosis and incompetence of the calcified tissue aortic valve with resulting LV hypertrophy and dilation along with pulmonary and systemic edema.

**Discussion Points**

Careful follow-up and multidisciplinary care (Cardiology/Internal Medicine, Obstetrics) during both the antepartum and postpartum periods, with a low threshold for cardiac reevaluation, are important for women with any structural cardiac disease.

In this case, early consultation with a multidisciplinary evaluation and involvement in the antepartum and postpartum care may have led to more timely recognition of her postpartum cardiac decompensation which may have ultimately improved her chance of survival. It is known that tissue cardiac valves deteriorate over time, particularly in younger persons, with the potential for acute or subacute valve failure [9]. The hemodynamic changes of pregnancy/puerperium may further increase the risk of a decompensation in this population. These patients therefore require careful follow-up.
Cardiac/Vascular - Case 3
A woman in her late thirties from rural Alberta, G4P3, had an eight year history of poorly-controlled hypertension and non-compliance. Her initial contact for prenatal care was at 32 weeks gestation, at which point her BP was markedly elevated at 180/145. She was hospitalized briefly for BP control, then readmitted at 35 weeks gestation and underwent a successful Cesarean delivery. Postpartum blood pressures at discharge remained high at around 160/100 on antihypertensive treatment. One day after discharge, the woman was found deceased at home. Postmortem exam revealed aortic rupture with hemopericardium.

Discussion Points
During this reporting period there were two maternal cardiac deaths (20%) due to aortic rupture (one antepartum and one postpartum). Pregnancy is known to be a period of enhanced risk for aortic rupture due to the enhanced shearing forces in the aorta (associated with increased cardiac contractility) as well as hormonally-mediated changes in the media of the aortic wall. The risk is much higher in women with severe hypertension or aortopathy (Marfan’s or Turner’s syndromes, coarctation of the aorta, etc.)[8]. Aggressive control of severe hypertension (particularly SBP > 160) and a high index of suspicion to investigate sharp, severe and tearing or migrating chest pain is needed in order to reduce the risk of maternal morbidity/mortality.

Cardiac/Vascular - Case 4
A young woman from northern Canada had a history of tuberous sclerosis with skin involvement as well as prior resection of a cardiac rhabdomyoma. Prior to pregnancy she had minimal LV dilation or dysfunction and a good functional status. During pregnancy she was followed closely and noted to have a significant decline in her cardiac function. In the peripartum interval she was monitored closely by cardiology, anesthesia and obstetrics and had a successful Cesarean delivery (due to fetal intolerance of labour). Medical follow-up with cardiology was suggested on discharge but did not occur, as the patient returned to her home community in remote northern Canada. Three and a half months later she presented to her local nursing station with chest pain and was noted to have been non-compliant with her furosemide and beta-blockers. She was reassured and discharged home but returned two weeks later with worsening chest discomfort and cough.

On transfer to a secondary medical centre she developed hypotension/shock and ended up in ICU, intubated and on vasopressor support. A repeat echo at this time confirmed extremely poor cardiac function. The patient then suffered a cardiac arrest and died. The postmortem confirmed “cardiac arrest due to septic shock.”
Discussion Points

This young woman with serious underlying cardiac disease received appropriate care and follow-up during the antepartum and peripartum periods, but was lost to follow-up post-partum (despite having experienced a significant pregnancy-associated decline in her cardiac function). This illustrates the issue of differential access to specialty care which is sometimes experienced by women living in rural and remote communities. The woman was non-compliant with her medical therapy and when she presented with concerning symptoms, the severity of her illness was not initially recognized. She then deteriorated and succumbed to a superimposed illness because of her severe cardiac comorbidity. In such cases, communication with community practitioners and dedicated efforts at ensuring appropriate medical follow-up are essential.

• Shared Learning – care of women with cardiovascular disease during and after pregnancy

• Practitioners must maintain a high index of suspicion for cardiac disease in pregnant women, as their symptoms may mimic those of normal pregnancy.

• Women with any structural cardiac disease require careful multidisciplinary care (Cardiology/Internal Medicine, Obstetrics, Anesthesia) and follow-up during both the antepartum and postpartum periods, with a low threshold for cardiac reevaluation.

• Severe hypertension (systolic > 160 and/or diastolic BP > 110) should be aggressively lowered in pregnant and postpartum women to reduce the risk of intracerebral hemorrhage and aortic dissection.

• Aortic dissection should be considered and investigated in pregnant women presenting with sharp and severe, tearing or migrating chest pain.

• Women with tissue cardiac valve prostheses may experience a valve degeneration/failure in pregnancy or postpartum, and their status should be monitored closely.

• Women with pulmonary AVMs are at risk for rupture during pregnancy. These lesions should be identified and dealt with prior to pregnancy, if possible, and followed closely by relevant experts during pregnancy.

• Dedicated efforts at ensuring appropriate medical follow-up and communication with community practitioners are essential in the postpartum care of women who have a chronic cardiac condition or who have experienced a cardiac complication during pregnancy.
References


Maternal Mortality secondary to suicide, drug overdose and homicide comprise a large category of the overall maternal loss statistics for the Alberta population. These three categories of maternal death causes considered here are distinct. The first two are more closely related to each other than the third. A review of data from the Canadian Maternity Experiences Survey (2011) found that the dimension of abuse during pregnancy was associated with postpartum depression [1]. In the United States (2012) conclusions from analysis of data from the United States National Violent Death Reporting system (NVDRS) describes the importance of mental health, substance use and intimate partner problems found with pregnancy-associated suicide [2]. Research findings published by Martin, Arcara et al (2012) reported women who were violated during pregnancy or the postpartum period are more likely than non-victimized women to use substances. Violence during pregnancy and postpartum has been linked to depression, anxiety and post-traumatic stress disorder. Some women become so depressed about the violence that they have suicidal thoughts or ideation [3].

Critically important statistics to consider in this report would be the occurrence of each of these three maternal loss causes during the pregnancy and postpartum interval relative to the incidence of female death in a control, non-pregnant, reproductive age population in the province. This comparison would shed important light if there is enhanced risk of death in the peripartum period.

Deaths secondary to suicide, drug overdose and homicide accounted for 26% of deaths of women during pregnancy or within one year after pregnancy in the Alberta inquiry population. In Alberta 40 women died from these causes between 1998 and 2011. The Maternal Mortality Working Group (MMWG) was unable to discern whether deaths of women from drug overdose were intentional or accidental in most of the drug toxicity cases. Information on these women was limited due to privacy and judicial limitations in access to data.

Of the women who died from suicide, drug overdose or homicide:
- 83.3% (n=10) of women who died from suicide and 77.2% (n=17) from drug overdose had a previous history of mental health concerns and/or history of substance use
- 41.2% (n=14) of women who died from suicide and drug overdose experienced a recent loss (fetal or infant death or death of significant other).
- 73.5% (n=25) of deaths from suicide and drug overdose occurred after 42 days post partum or termination of pregnancy
- Four deaths from homicide occurred during pregnancy
Suicide

The World Health Organization reports that every year almost one million people die by suicide. It remains a significant social and public health concern. In 2009 there were 3,890 suicides in Canada, a rate of 11.5 per 100,000 people [5]. Suicide was the leading cause of injury deaths in Alberta in 2010 [6]. The risk of suicide in females was 6.3/100,000 in the general female population in Alberta in 2009 [7]. Females age 15 -19 years (within the childbearing years) had a higher rate of self-inflicted injury/attempted suicide than males and other age groups.

Women in general are three times more likely to attempt suicide than males. However, males are four times more likely to complete suicide [5]. Moreover, self-harm thoughts are relatively common in pregnancy and postpartum (5-14 %) [8]. Distinguishing women who are at risk of suicide from those who suffer from self harm thoughts, although some women may be both, can be challenging and requires specialized services.

The suicide ratio for maternal deaths in Alberta is 1.92 per 100,000 deliveries for 1998-2011 combined. Suicide is one of the most common causes of maternal death in pregnancy and the first year postpartum in developed countries [9, 10, 11, 12]. In the UK, suicides in pregnant women were less common than in the general populations, whereas the postpartum rate was similar to non-pregnant populations. Similar to findings in Alberta, the majority of the women in the UK who completed suicide had a previous mental health history [13]. A wide range of factors – biological, psychological, familial, social, economic and cultural contribute to one’s resiliency or vulnerability to suicidal behaviour[14] including: mental and physical illness, alcohol or drug abuse, acute emotional distress, violence, history of sexual abuse, a recent adverse event or, in many cases, a combination of these factors [9]. In the UK over fifty percent of women who completed suicide were in stable relationships, were older than 30, had stable
mental health in pregnancy and were financially stable [15]. Also, more than 90% of the UK sample of women was caucasian. This emphasizes that in pregnancy, women with a previous mental health history need to be followed closely postpartum by specialized services.

Targeting mental health and addiction problems in pregnancy and postpartum could be a means for mitigating suicidal risk. A severe major depressive episode is a risk factor for suicide in the general population, as well as in pregnancy and postpartum. Major depression is one of the most common mental health concerns in this population and will be discussed below. Albeit anxiety disorders and post traumatic stress disorders are common in pregnancy and postpartum, their impact on suicide is poorly understood [16]. Post-traumatic stress disorder (PTSD) as a result of child-birth has been a recent topic of research [16]. Postpartum psychosis is also a very strong risk factor for suicide, especially in the early postpartum period, with that being the main diagnosis in 38% of the women who completed suicide in the UK [13]. Postpartum psychosis has been shown to occur in 1-2 of 1000 women who deliver and typically presents within the first week postpartum, although it can occur up to 3 months postpartum. It is a rapidly deteriorating condition that puts a woman at risk of infanticide, as well as suicide. A family history of Bipolar Affective Disorder, previous personal history of psychotic mood disorder, primiparity, perinatal death of infant or previous postpartum psychosis (>50% reoccurrence) elevates a women’s risk [6,13]. Moreover, women with chronic mental illnesses, in particular Bipolar Affective Disorder and Schizophrenia, need to be carefully monitored in pregnancy and postpartum, for a number of reasons, including that both are associated with suicide risk [17].

Around 8-12% of pregnant women and 10-16% of post partum women are affected by depression. [10,18] In 2004, the Capital Health Region reported 13% of postpartum women screened with the Edinburgh Postnatal Depression Scale were at risk for postpartum depression (8% scored between 10-13 “possible depression” and 5% scored over 13) [19]. Over 20% of the mothers who completed suicide in the UK had a main diagnosis of severe depressive illness [13]. There are a number of psychosocial and biological risk factors for a major depressive episode in pregnancy and postpartum. Poverty, migration, minority ethnic group, exposure to violence, low social support (especially partner support), previous miscarriage or pregnancy termination, unwanted conception, early childhood environment and certain personality factors are associated with postpartum depression [16]. Fetal death or the death of an infant in the first year after delivery was strongly associated with hospitalization for a suicide attempt in a study by Schiff and Grossman. Most attempts were the result of poisoning (63.5%) and were most frequent in the first and 12 months after delivery [6]. In Alberta 1998-2011, 40% of women who died from suicide and drug overdose experienced a perinatal loss.

Suicide by hanging was the second most common method of suicide for females in Alberta in data from 2001 to 2010 [6]. In the UK, 89% of the pregnant and postpartum women died by violent means, which included hanging [13]. This is strongly supported by the information of maternal deaths by suicide in Alberta. There were 12 cases of suicide identified in this inquiry eight women had a prior history of depression and seven with prior suicidal ideation and attempts. In the UK “almost half of the women who died from suicide might not have died if their
past history had been accurately identified and if plans for proactive management had been put in place. At the very least they should have received close surveillance for the maximum period at risk following delivery and perhaps prophylactic medication [15]."

**Suicide – Case 1**

A young primigravida woman with a previous history of suicidal ideation delivered a healthy term male infant with an uncomplicated peripartal course. She had seven prenatal visits and three “no shows” one month prior to delivery. She confided that she would be left alone with her newborn and a 5-year-old niece. She also notes that there was extensive substance and alcohol misuse among her family and friends. She was seen by Social Services during her postpartum stay in hospital. It was advised that close supervision be undertaken as this young mother had limited support systems. The chart reveals that she was “involved in a domestic dispute” and was found in an asphyxiated condition due to hanging. She left a suicide note that she had been planning suicide for a number of days. Her infant was approximately seven months old at the time of her death.

**Discussion Points**

The previous history of suicidal ideation put this young woman at increased risk for recurrence. A proactive approach preconceptually or early prenatally to outline her management of care following delivery was needed. The referral to social services was appropriate considering the concerns voiced by this young mother. However, a referral to psychiatry or a specialized perinatal psychiatry program (if available) could also have been instituted. A communication plan between hospital and community services outlining the monitoring and support this woman required prior to discharge may have been valuable in preventing this tragic outcome.

**Suicide - Case 2**

A woman in her early twenties was known to have a history of depression and drug misuse. There were numerous prior episodes of self-harm and suicide attempts. She had scarring on her wrist and neck from previous suicidal attempts. She was on antidepressant medication, and at 29 weeks pregnant she was found hanging. She was coded and transferred to hospital wherein an emergency caesarean section was undertaken for a stillborn infant. Subsequently the mother expired from asphyxia secondary to hanging. No drugs or ethanol were detected in her blood.

**Discussion Points**

Medical and midwifery practices should have a referral process to a specialized psychiatric perinatal service in place for women at risk. This woman was on antidepressant medications but it was not clear from the information available if she saw specialized psychiatric or addictions services.
Drug Toxicity

Poisoning by drugs was the leading method of suicide death for females in Alberta in 2010. Interpretation of the Alberta deaths reviewed due to drug toxicity was difficult as it was not possible to determine which cases were accidental versus intentional overdoses. Most of the women who died from drug toxicity had a history of significant substance abuse such as opioid dependence. Thirteen of 22 cases had multiple substances in their system including prescription medication, the most common being Tylenol 3’s.

Drug Overdose – Case 1

A woman in her twenties, gravida 2 para 1, had a Cesarean section at 39 weeks. She delivered a healthy male infant and her peripartal course was uncomplicated. She was known to use methamphetamine, opium and cocaine. She had been previously diagnosed with ADHD, and an eating disorder. She was hospitalized two months prior to her death for depression, increased suicidal ideation, anxiety, sleep disturbance, and binge eating. Psychiatric consultation was undertaken at that time.

One week prior to her death, she shared a friend’s fentanyl patch and became unconscious. She was brought to the hospital unresponsive, and was diagnosed with anoxic brain injury. She expired approximately one week following her admission to hospital. Toxicology results showed fentanyl and other illicit drugs in her system. Autopsy showed brain anoxia and cardiomegaly.

Discussion Points

This case history demonstrates the complexities in the lives of these women. This patient had a variety of mental health and dependency issues and was being followed by psychiatry services. Addiction programs geared towards pregnant and postpartum mothers monitored jointly by obstetrics and psychiatry may have proven valuable in this case.

Homicide

Abuse and violence against women of reproductive age is a serious public health concern. Women outnumber men as victims of assault by a spouse or partner. In Canada in 2011 intimate partner violence (IPV) where women are victims is 0.44/100,000, while the rate for men as victims is 0.08/100,000. Studies typically find that current and former intimate partners are the perpetrators of the violence. As demonstrated in this inquiry some women die from violence while pregnant and postpartum. The prevalence rate of physical violence in pregnancy varies but in the majority of studies it was 4 – 8% in developed countries. Tallieu and Brownridge, on reviewing the literature, found that 60 – 96% of women in various studies that experienced violence during pregnancy also experienced it before pregnancy. In fact one of the most consistent and strongest predictors of violence during pregnancy is having experienced violence prior to pregnancy. Those women violated during pregnancy and postpartum are more likely than non-victimized women to use substances, including alcohol, prescription drugs and illicit drugs. Partner violence increases the risk of depression and suicide attempts. In Canada, 21% of women abused by a
partner were assaulted while pregnant. Of the women who were abused, 43% report the abuse began during pregnancy [24, 29]. Antenatal care provides a window of opportunity for the identification of those women who are experiencing intimate partner violence (IPV). Practitioners need to be certain to screen for IPV.

Unfortunately, as a result of the judicial nature of the deaths due to homicide little information is available to the MMWG. Of the women who died in 1998-2011 in this inquiry, 75% of deaths from homicide occurred during pregnancy. It is known from media coverage that two of the six homicide cases were a result of IPV. Both women died early in pregnancy limiting the time these women had to access prenatal care. These cases reflect the importance of screening for IPV preconceptually and at annual physical check ups.

**Shared Learning - care of women at risk for suicide, drug toxicity and homicide during and after pregnancy**

- Thorough history and screening preconceptually and early in pregnancy to identify risk factors: substance use/abuse, suicide ideation or attempts, mental illness, domestic violence, sexual abuse and lack of social support.

- Early referral and improved access to mental health resources, addiction services geared towards pregnant and postpartum women with ongoing follow-up.

- Referral to support services for women experiencing domestic violence.

- Improve access to shelters and safe houses for women.

- Proactive approach outlining a plan and management for care throughout pregnancy and postpartum for women at risk for suicide, drug use and domestic violence.

- Screening with Edinburgh Postnatal Depression Scale at 6 weeks post-partum among all mothers. Question 10 (suicidal ideation) affirmative responses should be followed by an evaluation of suicidal ideation, plan and intent. Scores > 10 suggest follow-up in two weeks.

- Establishment and/or referral to specialized psychiatric unit for pregnant and postpartum mothers to provide treatment while allowing bonding with newborns. The woman’s progress should be monitored jointly by obstetricians and psychiatrists.

- Improved access to bereavement support in hospital and the community for women experiencing a perinatal loss.

- Limiting access to polypharmacy/ multiple prescriptions.

- Centre for opioid dependent pregnant women monitored jointly by obstetricians and psychiatrists.
References


4. Patrick K. It’s time to put maternal suicide under the microscope. CMAJ 2013.


Other Resources


Cancer is diagnosed in 0.02-0.1% of pregnancies with an estimated incidence of 1:6000 live births. The prevalence is expected to rise in developed countries due to an increase in maternal age [1]. Malignancy-related mortality is generally classified as coincidental. A coincidental death is defined as death due to conditions occurring during pregnancy, where the pregnancy is unlikely to have contributed significantly to the death, although it is possible to postulate a distant association [2, 3]. The UK Enquiry classifies deaths to some cancers, such as breast, as indirect, where the hormonal changes in gestation might have precipitated disease progression [4]. Most malignancies are not affected by pregnancy and the prognosis is similar to that in stage-matched non-pregnant women.

The diagnosis of cancer in pregnancy is difficult and one should keep a high index of suspicion. Cancer related symptoms may be mistaken for common physiologic changes of pregnancy. Some examples include, but are not limited to nausea, abdominal discomfort, difficulty breathing, changes in bowel habits, back pain. In addition, diagnostic modalities are somewhat limited due to concerns regarding radiation exposure. Treatment is equally challenging and the goal is to offer the best treatment to the mother while limiting exposures to the fetus.

From 2002 – 2011, there were 22 malignancy related deaths in Alberta identified that met the study criteria. Table 1 outlines the different types of cancer by system. All but four cases occurred in the late post-partum period (more than 42 days but less than 365 days since delivery). Maternal mortality is a catastrophic event, thus on-going detailed review is essential to ensure improvement in the quality of care.

<table>
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<th>Type of Cancer</th>
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<td>&lt; 42 days</td>
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**Breast cancer** is the leading cause of death due to cancer in women of reproductive age and in pregnancy it is estimated to occur with a frequency of 1:3000 [5]. Most cases are of the invasive ductal type and tend to be diagnosed at more advanced stages in pregnancy due to delays in diagnosis. Of the five cases observed in Alberta, three were primary and two were metastatic.

One multiparous patient had no prenatal care and presented at 38 weeks for delivery. Six months later she was diagnosed with invasive ductal carcinoma with metastasis to bone and liver. Her symptoms were present for six months, but she did not seek medical care.

**Breast Cancer - Case 1**

A woman in her thirties, G2P1, presented with complaints of a small right breast lump at 25 weeks. Her risk factors included a previous abnormal PAP requiring colposcopy. The breast lump was not further investigated at the time and the pregnancy went on to term. She delivered a healthy, infant. At the post-partum appointment the lump was unchanged in size. One month later she was diagnosed with a right sided invasive ductal carcinoma of the breast. She had a mastectomy and axillary node dissection shortly after and the pathology confirmed the diagnosis of high grade ductal carcinoma (Grade III/III) with extensive lymphatic involvement (5/10 right axillary nodes involved). She then underwent 3 courses of chemotherapy (5-Fluorouracil, Epirubucin and Cyclophosphomide) followed by Tamoxifen and Chlorondate maintenance. Three months after the completion of chemotherapy a bone scan and liver biopsy demonstrated metastatic disease. Within a month she developed significant pulmonary symptoms (short of breath (SOB), hemoptysis) and was admitted to the hospital. She required palliative sedation to manage her intractable pain. She passed away just 11 months after the birth of her baby.

**Discussion Points**

This case emphasizes the importance of following up on unusual breast lumps during pregnancy. Most breast lumps are benign (~80%) and blocked lactiferous ducts are a common occurrence. Ultrasound is a widely accepted diagnostic modality in pregnancy and it is a useful initial step in the investigation of a breast lump. Further follow-up studies include mammography and tissue biopsy.

Early referral and diagnosis is imperative as treatment can be initiated during pregnancy. The Royal College of Obstetrics & Gynecologists (ROGC) recommends prompt referral to a breast specialist team and appropriate imaging for women presenting with a breast lump in pregnancy [6].
**Breast Cancer - Case 2**

This woman in her early forties, G1P0, had a history of a high grade aggressive breast cancer that was treated prior to the index pregnancy. The treatment consisted of bilateral mastectomies and chemotherapy, which were completed one year prior to the pregnancy. The metastatic work-up was negative at the time of conception. The pregnancy was uneventful and she gave birth at term healthy infant. A month after delivery she presented with significant back pain which was initially thought to be related to the pregnancy. Another three months later she was referred back to her oncologist and extensive bony metastasis was diagnosed on the bone scan. She received prompt radiation to control her symptoms. She was then started on Herceptin and Taxol but went on to develop clinical signs of cord compression. At the time of death she had metastatic disease compressing her spinal cord at the T9 level as well as significant liver involvement. Her baby was six months old.

**Breast Cancer - Case 3**

This woman in her late twenties, G1P0, had a history of right sided breast cancer treated with a lumpectomy and four cycles of chemotherapy and radiation in another province. She did not receive Tamoxifen. Her treatment was completed approximately one year before she became pregnant. Her pregnancy was otherwise uncomplicated and there are no suggestions of unusual symptoms. She gave birth at 40 weeks to a healthy infant. Four months post-partum she presented with shortness of breath, chest tightness, headache, abnormal peripheral vision and nausea. Another three months later she was seen by a respirologist who found a left breast mass, enlarged liver and tender abdomen. A bone scan was performed immediately and demonstrated extensive metastasis. Within less than two weeks she died secondary to hepatic encephalopathy. Her newborn baby was seven months old and the breast cancer diagnosis was first made three years prior.

**Discussion Points**

Cases 2 and 3 are unfortunate examples of cancer recurrence during pregnancy. A high index of suspicion should be maintained in order to identify symptoms that may suggest disease recurrence, but are otherwise normal in young healthy pregnant patients. Direct interviewing regarding such symptoms may be reasonable, as patients might not know to differentiate pathological symptoms from normal pregnancy changes. Prompt referral to a multidisciplinary team experienced with cancer in pregnancy should be initiated.

Ideally, all women who suffered a malignancy should have a pre-conceptual counselling appointment with a Maternal Fetal Medicine specialist. Currently, it is recommended that women with a prior history of breast cancer should wait at least two years after treatment cessation before conceiving [6, 7]. Those with a good prognosis may shorten this interval. For high risk
patients, the delay may be even longer in order to allow for the recommended recurrence preventative treatment with Tamoxifen, which is five years.

**Breast Cancer - Case 4**

This woman in her late thirties, G2P1, noticed an enlarged supraclavicular node at 14 weeks gestation. She is otherwise healthy, her only risk factor being an increased BMI of 30. The supraclavicular node was biopsied two months later and revealed an undifferentiated carcinoma with positive estrogen and progesterone receptors. It was treated like a metastatic cancer of unknown primary. In order to facilitate diagnosis and avoid radiation exposure in pregnancy, delivery was planned at 30 weeks. After administration of steroids for fetal lung maturation, a healthy infant was delivered by Cesarean section.

Following delivery the metastatic work-up was completed and revealed a small (~0.6cm) poorly differentiated ductal carcinoma of the breast with positive ER/PR, without metastasis except the neck. She was treated with three cycles of chemotherapy (FEC) but did not respond adequately. She developed toxicity to Docetaxol and the disease progressed despite being placed on Capecitabine. She was about seven months post-partum when it was noted that she had significant metastatic disease in both abdomen and thorax. She died two months later of respiratory failure.

**Discussion Points**

This unfortunate case demonstrates a timely diagnosed aggressive carcinoma that was refractory to treatment. The increased BMI might have played a role in the late identification of an enlarged supraclavicular lymph node. On the other hand, the initial pregnancy visit helped make the diagnosis.

It is unclear from the chart why the cancer was initially classified as unknown primary, when the positive ER/PR raised a high index of suspicion for breast carcinoma. When a cancer is suspected in the early third trimester, prompt delivery to facilitate maternal diagnosis and treatment is a very accepted and reasonable option. Considering how aggressive this malignancy was and its dissemination to distant lymph nodes at the time of diagnosis, it is unlikely that a different practice would have affected the outcome.

**Hematologic Malignancies**

**Hematologic cancers** are uncommon in pregnancy, with lymphoma being the most common cancer and the fourth most common cancer in pregnancy, with an estimated incidence of 1:6000 [8]. The majority of cases are classic nodular-sclerosis Hodgkin’s lymphomas, the most common subtype in women younger than 40 years. The presenting symptoms are shortness of breath or hypermetabolism, which can also occur in normal pregnancies. Furthermore, the diagnosis is challenged by limitations in imaging.
Leukemias are rare in pregnancy (1:750000-100000) and are usually acute, involving either myeloid or lymphoid cell lines. When they occur, they need to be treated immediately to ensure good maternal prognosis [8].

From 2002-2011, there were three hematologic malignancy related maternal deaths encountered in Alberta: One acute lymphocytic leukemia (ALL) and two Hodgkin’s lymphomas.

**Hematologic Cancer - Case 1 & 2**

One non-English speaking patient presented late for prenatal care and she had an uncomplicated course. Delivery occurred by CS and all CBC’s were normal pre and immediately post-partum. Two months after her CS she presented with fever and the work-up revealed ALL. Despite prompt and appropriate chemotherapy treatment she died within one year post-partum due to respiratory failure secondary to aspiration.

Another patient with a three year history of neutropenia, presented five months after an uncomplicated pregnancy and delivery with pleural effusion, neutropenia, anemia and lymphadenopathy. A bone marrow aspirate was inconclusive. A month later, a difficult axillary node biopsy revealed a Hodgkin’s lymphoma. She died two months after the diagnosis due to sepsis.

**Discussion Points**

These two cases illustrate the fact that hematologic malignancies are difficult to diagnose. In pregnancy, we have the unique opportunity to perform serial CBC’s on otherwise healthy women, thus it is of outmost importance to follow up any unusual results with consultation to appropriate specialists (Hematology, Internal Medicine, Maternal Fetal Medicine).

**Hematologic Cancer - Case 3**

This woman in her thirties, G1P0, was diagnosed with Hodgkin’s lymphoma in the late first trimester (~16 weeks). She presented with large left neck adenopathy. The diagnosis was made with an excisional biopsy. Due to the pregnancy, an MRI was performed and identified bulky cervical and thoracic adenopathy with no disease below the diaphragm, which corresponds to stage 2A.

A bone marrow biopsy was also performed and it was clear of disease. Fetal anatomy was confirmed to be normal. Maternal treatment was planned with single agent vinblastine. After the second dose her symptoms worsened requiring steroids. At this point the pregnancy was ~24 weeks and interval growth was appropriate. ABVD was discussed and started promptly as the maternal symptoms were not improving and the neck mass was enlarging.

Delivery was induced at 34 weeks due to the maternal malignancy and a healthy baby. Six weeks post-partum a D&C was required for retained products. A staging CT was performed immediately post-partum and demonstrated regression of the masses. Within two months the cancer was found to progress despite chemotherapy.

After five courses of ABVD, the chemotherapy was changed to GDP and stem cell transplant as the disease was no longer responsive. There was a temporary plateau in disease progression.
after the high dose chemotherapy; radiation was also administered. She then developed a large thoracic consolidation which was exerting mass effect on the heart resulting in pleural and pericardial effusions. This culminated in an ICU admission and inability to be weaned off the ventilator. Care was withdrawn five days before the first birthday of her baby boy.

Discussion Points

It appears that in this case the literature-recommended treatment for Hodgkin’s lymphoma (ABVD) was delayed due to fetal concerns (single agent chemotherapy should only be used in the first trimester as a bridge to multi-agent chemo). Combination chemotherapy is usually avoided in the first trimester due to concerns regarding teratogenicity. In the second and third trimesters on the other hand, maternal treatment should occur by the same regimen administered to non-pregnant women, while monitoring fetal growth and well-being [8].

Brain Cancer in Pregnancy

Brain cancers are very rare in women of reproductive age (incidence of 2-3.2:100000), placing them outside the 10 most common malignancies. Gliomas and meningiomas are the most common types. The diagnosis is generally made by MRI. Surgical treatment is not contraindicated. The management plan should be individualized [9]. Two cases of brain cancer related maternal mortality were encountered in Alberta during the index period. Both appeared particularly aggressive.

**Brain Cancer – Case 1**

A woman in her thirties was diagnosed ten months after a normal SVD with a malignant astrocytoma. She presented with a history of headache, ataxia, loss of short term memory and motivation. A craniotomy was performed due to her early age, but she died of malignancy complications (uncal herniation, damage to the midbrain and thalamus).

**Brain Cancer – Case 2**

A woman in her late twenties, G3 P2, was diagnosed with a malignant glioma in early pregnancy. She declined chemotherapy and was treated with steroids and anti-epileptic medication. She was an inpatient for most of the pregnancy due to her declining neurological status. Delivery occurred at 31+4 weeks by CS as the maternal status was further deteriorating. A healthy female infant of 1440 g was born. Post-partum the patient’s management was palliative as she did not regain consciousness and she died two months later.
Gynecologic Cancers in Pregnancy

Cervical and ovarian cancers are the most common gynecologic malignancies diagnosed in pregnancy. Endometrial cancers are sometimes diagnosed incidentally at the time of dilatation and curettage and vulvar cancers are very rare [10]. Two gynecologic cancers were encountered in Alberta between 2002 and 2011, one small cell carcinoma of the cervix and one recurrent mucinous ovarian carcinoma.

Cervical cancer
The incidence of abnormal cervical cytology diagnosed in pregnancy is approximately 1-5%. The diagnosis and management should follow the same guidelines as in non-pregnant women. Low grade lesions are more likely to regress during the pregnancy (48-62%) as compared to high-grade lesions (27-34%). Colposcopic follow-up should occur every trimester for patients without evidence of invasion. Cervical conisation should be avoided in late pregnancy due to potential complications such as bleeding, rupture of membranes or preterm labor.

Cervical cancers are encountered in 1-12:10000 pregnancies. The management depends on tumor characteristics, spread and gestational age. MRI is the best imaging procedure for the diagnosis of local or regional spread. Small cell carcinoma has a particularly poor prognosis; the other types of cervical cancer should be managed similar to the non-pregnant state. The French and European Working Groups have suggested algorithms for the management of these cervical cancers, by stage and gestational age [11, 12].

Cervical Cancer – Case 1
This woman in her thirties, G1P0, presented at 26 weeks with symptoms of spontaneous rupture of membranes. This was not confirmed by US as the amniotic fluid volume remained normal. Since her symptoms persisted, she had a speculum exam in the office when a small cervical polyp was noted. She subsequently developed vaginal bleeding. The cervical polyp grew rapidly from 2 cm to more than 10 in the span of a couple of weeks. A biopsy showed a small cell cervical cancer.

At 28 weeks she had a caesarean section and radical hysterectomy, in order to relieve her gastrointestinal and urinary symptoms related to the great tumor burden. Post-partum she had four cycles of cisplatin and atopicide as well as radiotherapy to her pelvis and paraaortic region. Post-treatment suggested complete remission. Within a few weeks she developed neck and epigastric adenopathy as well as documented extensive liver metastasis. As her status was deteriorating on a daily basis she was admitted and received rescue chemotherapy with Carboplatin and Taxol. Unfortunately she died six days later, or six months after the birth of her child.

Discussion Points
This case illustrates a very rare and aggressive type of cervical carcinoma which progressed rapidly despite appropriate obstetrical and oncological care. Of note, the diagnosis was made possible by the speculum examination performed in the context of antenatal bleeding. It is very important to perform such an assessment in patients with antenatal bleeding as it may be the only presenting symptom of cervical cancer, although in this case it probably wouldn’t have changed the outcome.
Ovarian Cancer

Ovarian masses diagnosed on routine US in pregnancy are generally benign: about 1:600-1500 such masses require surgery and of those 1-3% are malignant. Most commonly, these tumors are of the non-epithelial type or low malignant potential. The management is guided by the tumor type, stage, gestational age and family wishes.

Epithelial-type ovarian cancers are generally treated surgically with a staging laparotomy and debulking procedure. During pregnancy, such an operation cannot be completed fully unless the pregnancy is terminated. Chemotherapy is also part of the management protocol and there have been reports of good neonatal outcomes following treatment in pregnancy.[10]

Ovarian Cancer – Case 1

This woman in her thirties, G1P0, was diagnosed with Stage 1A mucinous ovarian carcinoma about 1 year prior to her pregnancy. She was then treated with oophorectomy, staging laparotomy and chemotherapy (4 courses of carboplatin). A few months after the completion of her treatments she presented with lower back pain that was not further investigated radiographically because she had a positive pregnancy test. It is unclear as to the outcome of this pregnancy test as her index pregnancy was only conceived three months after the low back pain was identified.

Starting in the first trimester her pregnancy was complicated by hypertension and nausea and vomiting. This progressed to weight loss and inability to maintain oral feeds. At 20 weeks gestation an MRI was performed to evaluate her weight loss and abdominal pain and extensive cancer recurrence was diagnosed: there was extensive pelvic, abdominal and mediastinal lymphadenopathy and metastasis to ribs. She was treated promptly with Carboplatin and Taxol as well as an ureteric stent to release an obstruction. At 27 weeks it was noted that the baby was suffering from severe placental insufficiency and IUGR and a caesarean section was performed.

Post-partum the mother was managed palliatively and she succumbed under palliative sedation due to significant pain from her malignancy only two months after the birth of her baby.

Discussion Points

This case illustrates first and foremost that a positive pregnancy test should not preclude investigations where metastasis or recurrence is suspected. In addition, patients with a history of malignancy should be strongly advised to postpone pregnancy until they have been in remission for two years.
Gastrointestinal Malignancies in Pregnancy

There is a paucity of literature regarding gastrointestinal malignancies during pregnancy. However a report from the United Kingdom between 2003 and 2005 revealed that 13 of 82 (15.8%) maternal malignancy-related deaths were due to gastrointestinal cancers [2]. During the period of January 1, 1998 to December 31, 2011 there were five maternal deaths due to gastroesophageal cancers, two due to colon cancer and one due to adenocarcinoma of unknown primary that appeared to represent a cholangiocarcinoma. This represents 36% of all maternal deaths due to malignancy. All diagnoses were stage IV at diagnosis and one was considered as an **Indirect** cause of maternal mortality and seven were deemed **coincidental**[15].

**GI Cancer – Case 1**
A woman in her twenties, G4P3, was admitted to a tertiary centre at 26 weeks gestation for investigation of gastric thickening and ascites. During the prior three months, she had ongoing problems with right upper quadrant pain, nausea, vomiting, anorexia and 35 pounds weight loss (although limited documentation was available on her prenatal record). Initially these symptoms were interpreted as cholelithiasis of pregnancy (based on an ultrasound at 18.5 weeks gestation), however a repeat ultrasound revealed gastric wall thickening and moderate ascites. Endoscopy showed a mass in the body of the stomach which was biopsied and confirmed a mucinous adenocarcinoma with signet ring cells. Further workup identified distant spread of her cancer involving the omentum and ascitic fluid. At 28 weeks, the patient spontaneously delivered a stillborn. The patient did not receive anti-cancer therapy and approximately 1 month after delivery, the patient succumbed to her illness at hospice.

**Discussion Points**

In North America, the incidence of gastric cancer is low and accurate assessments of the incidence during pregnancy are lacking. Conversely, in South East Asia, there is a high incidence of gastric cancer which has resulted in implementation of screening programs for this disease[3][16]. In a review of the existing literature, Sakamoto et al. [4] identified 137 pregnancy-associated gastric cancers (the majority from Japan). Ninety two percent were diagnosed at an advanced stage and the two year survival rate was 15%. A diagnosis of gastric cancer in pregnancy is often difficult since symptoms of anorexia, nausea and abdominal pain may be attributed to normal pregnancy changes as opposed to symptoms of malignant disease. Unfortunately, the majority of patients have incurable disease when they become symptomatic from their gastric cancer.

Further, the finding of signet ring cells is also associated with a particularly poor prognosis [5]. Progressive nausea and vomiting and weight loss outside the first trimester is of concern in this case and involvement of an obstetrical specialist may have been indicated, although it was unlikely to have changed the outcome.
**GI Cancer - Case 2:**

A woman in her twenties, G2P1, was admitted to a tertiary hospital at 36 weeks gestation with persistent fatigue and nausea. An ultrasound of the abdomen was performed and revealed multiple lesions in the liver. According to her prenatal record, she was not gaining weight and in fact she had lost two kilograms from 14 weeks to 34 weeks gestation. There was also note of RUQ pain at 29 weeks which had resolved at week 30, but recurred a few weeks prior to presentation. An MRI on admission to hospital revealed that the left lobe of the liver was completely replaced with tumor and a 5 cm mass was present in the right lobe of liver. A subsequent liver biopsy confirmed metastatic adenocarcinoma. After delivery, the patient underwent a colonoscopy which revealed a mass in the descending colon as well as a CT scan which revealed lung metastases. On further history, she had bleeding per rectum since the birth of her first child (1.5 years) however, did not seek medical attention as she thought it was due to hemorrhoids. Due to her young age and a family history of colon cancer, the patient was referred for Genetics testing (results unknown). Mismatch repair protein profile analysis from her liver biopsy specimen was normal. After consultation with oncology, she was started on FOLFIRI chemotherapy three weeks post partum, and completed four cycles prior to disease progression. Capecitabine plus oxaliplatin was then administered however her disease progressed within five months and the patient passed away nine months after delivery.

**Discussion Points**

**Colorectal cancer (CRC)** during pregnancy is a very rare event with an estimated incidence of 0.002%. In a study by Dahling et al. [6], neonatal and maternal outcomes were compared between pregnant women with and without colorectal cancer in California between 1991 and 1999. A total of 134 CRC cases were identified for a rate of 0.028/1000 births. The majority were diagnosed postpartum (N=103) and women over 40 had a higher risk compared with less than 30 years (OR 11.3). There was no difference in neonatal outcomes aside from lower birth weight and prematurity. In a comparison to an age-matched, non-pregnant population with CRC from the California Cancer Registry, there was no difference in cancer stage, site or histology. However pregnant women with CRC were less likely to receive chemotherapy. Although there was a high death rate overall (43%), there was no difference in survival between the two groups.

It is unclear if this woman’s rectal bleeding was reported to medical care providers; this finding, in addition to weight loss into the second and third trimester, are common clinical manifestations of colorectal cancer. The mismatch repair immunohistochemical analysis suggests that this lady did not have Lynch syndrome.
**GI Cancer - Case 3:**
A woman in her thirties, G7 P3, presented to a tertiary hospital at 34 weeks gestation with premature rupture of membranes (PROM). The patient had presented for very few prenatal visits and was admitted to hospital at 30 weeks gestation for dizziness and a seizure (left against medical advice).

Due to PROM and a prolapsed umbilical cord, an urgent cesarean section was performed. Post operatively, she developed acute anemia (hemoglobin 68 units) and an abdominal CT scan identified a 12.9 x 8.4 cm mass in segments 2/3 of the liver and ascites. A subsequent liver biopsy confirmed an adenocarcinoma with an immunohistochemical profile most in keeping with a cholangiocarcinoma.

Due to ongoing problems with abdominal pain, nausea and psychological distress she was admitted to a tertiary palliative care unit and passed away approximately four months after delivery of her fourth child.

**Discussion Points**

**Cancers of unknown primary (CUP)** represents approximately 5% of all invasive cancers, with the most common histology being adenocarcinoma[17]. Initial evaluation of CUP should involve a complete history and physical exam, complete blood count, basic chemistries, and radiographic imaging of the chest, abdomen and pelvis. Women should also have a pelvic exam and mammogram, while men should undergo a prostate exam and the measurement of a prostate specific antigen. Finally, sampling of the tumor gives further information on histology and immunohistochemical profile.

In this case, the immunohistochemical profile and CT scan findings were suggestive of an unresectable intrahepatic cholangiocarcinoma. The most common risk factors for this rare tumor include primary sclerosing cholangitis, fibropolycystic liver disease, parasitic disease and viral hepatitis. The lack of sufficient prenatal visits may have contributed to the late stage of diagnosis of this disease.
Shared Learning – care of pregnant women with Cancer

- Clinical symptoms of cancer mimic normal pregnancy symptoms. A high index of suspicion should be kept and persistent or unusual symptoms should be further investigated.
  - Symptoms of weight loss and nausea outside of the first trimester require investigation and referral to Maternal-Fetal Medicine and an obstetrician.
- Women diagnosed with cancer in pregnancy should be cared for by a multidisciplinary team specialised in the area. This team should include oncologists and/or hematologists (depending on the cancer), maternal fetal medicine specialists, genetics, family physicians, psychologists, and social workers (Adapted from the SOGC recommendations on Cancer Chemotherapy and Pregnancy) [13].
- The imaging modalities of choice for diagnosis or metastatic work-up in pregnancy are MRI and US. X-rays and mammography can be used when indicated with appropriate shielding.
- Multiple chemotherapy agents have been used in pregnancy and are generally safe when administered after the period of organogenesis (>14 weeks)[13].
- If surgery is necessary, it should be performed in the second trimester.
- Radiotherapy is generally contraindicated in pregnancy, but exceptions do exist.
- Patients with a personal history of cancer should wait two years until attempting conception. Ideally, a pre-conceptual referral to a perinatologist should be undertaken.
References
Appendices
### Appendix A

Deaths Reviewed by the Perinatal Quality Assurance Sub-Committee & Maternal Mortality Working Group
1998 to 2011

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<td>7</td>
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<tr>
<td>2011</td>
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<td>19</td>
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<td>6</td>
<td>10</td>
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<tr>
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<td>158</td>
<td>34</td>
<td>58</td>
<td>66</td>
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</table>
# Appendix B

## Alberta Maternal Mortality Ratios per 100,000 Live Births
While Pregnant of ≤42 Days After Pregnancy

1998 to 2011

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Livebirths</th>
<th>Total Deaths&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Direct Deaths</th>
<th>Indirect Deaths</th>
<th>Combined Direct &amp; Indirect</th>
<th>MMR</th>
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<td>37947</td>
<td>9</td>
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<td>51</td>
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</tbody>
</table>

<sup>3</sup> Total deaths includes direct & indirect maternal deaths, coincidental & unspecified deaths
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