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A Systematic Review of Bacillus anthracis in Pregnant and Postpartum Women

Dana Meaney-Delman

Abstract

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A Systematic Review of *Bacillus anthracis* in Pregnant and Postpartum Women

(under the direction of Sheryl Strasser, GSU Institute of Public Health)

Bacillus anthracis, commonly known as anthrax, remains a public health concern. Medical countermeasures for anthrax include the use of antibiotics, vaccines and antitoxins, for post-exposure prophylaxis (PEP) and treatment. Guidelines for the use of these measures, initially developed by the Centers for Disease Control and Prevention (CDC) in 2001, are currently undergoing revision. Provisions for pregnant and postpartum women are considered in the existing CDC recommendations, but are based on limited evidence. Given that there are 7 million American women pregnant each year, a large-scale anthrax attack, could result in many of these women becoming exposed or infected. Understanding the natural history of anthrax in pregnant and postpartum women is critical for emergency preparedness planning. This systematic review will describe the worldwide experience of *B. anthracis* infection in pregnant and postpartum women and will inform new anthrax guidance.

INDEX WORDS: B. anthracis, anthrax, pregnant, postpartum

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Dedication

This manuscript is dedicated to my husband, Keith Delman, whose tireless efforts and support were critical to the success of the project.

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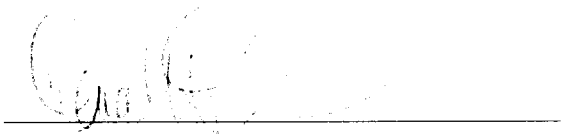

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Chapter I. - Introduction

In 2001, the United States experienced an anthrax bioterrorist attack involving *Bacillus anthracis* spores disseminated via the postal system. As a result, twenty-two people became infected with anthrax, of which eleven people developed inhalational anthrax, and five died from this deadly form of the disease (Jernigan et al. 2002; IOM 2011). In addition, eleven people exposed to anthrax developed the cutaneous form of the disease (Wright et al., 2010). The United States Public Health Service (USPHS) rapidly responded to the event, enlisting the assistance of the Centers for Disease Control and Prevention (CDC) and the Office of Emergency Preparedness (Montello et al., 2002). The event was a small scale attack, but as a consequence, political leaders, public health officials, clinicians, and the public became aware of the potential for this agent to be used as a biological weapon and this prompted extensive biodefense research (Wright et al., 2010). Although *B. anthracis* was investigated as an agent of biological warfare, dating back to World War I, the actual use of it as a bioweapon in the United States prompted the incorporation of bioterrorism into emergency preparedness planning (Wright et al., 2010).

The anthrax event occurred less than one month after the September 11 attacks, and together these terrorist acts set in motion a national emphasis on emergency preparedness (Wright et al., 2010), whereby anthrax became a major focus of the Working Group on Civilian Defense. After extensive analysis, this group concluded that if *Bacillus anthracis* was intentionally released over a large city, it would cause disease

and deaths in sufficient numbers to gravely impact the population (Inglesby et al., 2002).Given the difficulty in predicting, detecting or preventing a biological attack, anthrax preparedness continues to remain a national priority.

The Centers for Disease Control and Prevention, along with other federal agencies, has led the public health effort to prepare for an anthrax attack by promoting awareness, defining diagnostic criteria and developing medical and environmental countermeasures. The CDC published the first recommendations for anthrax treatment and post-exposure prophylaxis, immediately following the 2001 attack, which included specific modifications for pregnant and postpartum women. In addition to the CDC's decade-long efforts, other federal agencies, such as the National Institutes of Health (NIH), and the Food and Drug Administration (FDA) have been involved in the development of medical countermeasures against anthrax. In 2004, Project Bioshield established permanent funding for the purchase of medical countermeasures, provided money for research related to bioterrorism, and gave the FDA new authority for the use of new medical interventions for bioterrorist agents, under the Emergency Use Authorization (EUA). Anthrax was and continues to be a top priority agent and as such, the Strategic National Stockpile, a CDC- managed repository of medications for national emergencies is equipped with supplies for this particular biologic agent (Meadows 2004).

As a result of continued concern for the threat of anthrax, a national meeting focused on anthrax was convened in 2006, sponsored by the CDC, in collaboration with the Southeastern Center for Emerging Biologic Threats. The purpose of the meeting was

bring together anthrax subject matter experts to review research developments pertaining to anthrax countermeasures, and to redefine or reaffirm the previous CDC anthrax guidance documents (Stern et al., 2008). The proceedings of this meeting were published, with some revisions of the guidance for post-exposure prophylaxis and treatment of anthrax, both for the general population, as well as for pregnant and lactating women (Stern et al., 2008). The 2006 consensus guidelines not only addressed antibiotic recommendations but began to address the use of the anthrax vaccine in a post-exposure setting.

In 2001 and 2006, the clinical recommendations for pregnant and lactating women generally paralleled those of the general population. However, a special provision in the guidance prioritized the use of an additional antibiotic, amoxicillin, a drug with a great deal of safety data for pregnant and lactating women, above other agents. This antibiotic was only to be used after the acute threat of severe illness had past and, only if the *B anthacis* strain was proven susceptible. Also, in 2006, the use of anthrax vaccine was not recommended in pregnant and postpartum women, due to the dearth of safety data evaluating vaccine use in these women (Stern et al., 2008).

Subsequently, the Advisory Committee on Immunization Practices (ACIP) convened in 2007 to address new data that had emerged on the safety and immunogenicity of anthrax vaccine (AVA). At this meeting, the ACIP developed updated recommendations for the use of anthrax vaccine in the pre- and post-exposure setting, with modifications to the dosing and the route of administration. After examining new evidence, the ACIP recommended the vaccine as post-exposure prophylaxis for the general population, as well as for pregnant and lactating women (Wright et al., 2010).

The documents generated from these meetings, published in 2008 and 2010, currently serve as the mainstay of a public health response in the event of an anthrax attack.

In April 2011, the CDC began re-evaluating the medical countermeasures guidance related to anthrax preparedness, and to this end, has convened two recent meetings. The first meeting, in October 2011, focused on anthrax treatment and the second meeting, in March 2012, focused on post-exposure prophylaxis and antitoxins. During these meetings, the CDC and outside experts reviewed new antibiotic data, analyzed the most recent naturally-occurring anthrax cases (Walsh et al., 2007; Booth et al., 2010;MMWR, 2006; MMWR 2009), and examined experimental animal studies, to identify any new methods that could be used to effectively treat and prophylaxis against *B. anthracis* infections. The meetings included stakeholders from multiple federal agencies along with the CDC, including USAMRID, BARDA, NIH and the Food and Drug Administration (FDA). Ultimately, the discussions at these meetings will form the basis of information the Anthrax Management Team (AMT) at CDC will use as they formulated the new guidance.

At both of the recent anthrax meetings, and as part of the overall effort to revise the anthrax guidelines, even greater emphasis has been placed on addressing the special considerations of pregnant and postpartum women than has been in the past. By federal law, the Pandemic and All Hazards Preparedness Statute of 2006, preparedness planning must include the special needs of pregnant women, defined as an "at-risk population"

(Pandemic, 2006). Recent experience with another public health emergency, H1N1 pandemic flu, highlighted the many unique challenges posed by the maternal-neonatal dyad (Mosby, Rasmussen et al., 2011). In addition, the experience with pandemic flu fully established the importance of pre-event planning, specifically to address the complex needs of these women (Mosby, Ellington, et al., 2011). The fact that pregnant women developed more severe disease with higher mortality rates than the general population in the pandemic emphasized there are complex physiologic changes related to infectious diseases in pregnancy, which may influence how these diseases manifest (Loiue et al., 2011; Mosby, Rasmussen et al., 2011).

Although the previous guidance for anthrax has included provisions for obstetrical populations, recommendations for post-exposure prophylaxis and treatment did not address distinctive issues for pregnant and postpartum women, beyond modifications of antibiotics for safety concerns. Little is known about *B. anthracis* infection in pregnant and postpartum women, partly because this infection is rare, even as a naturally-acquired infection. By studying anthrax cases, a better appreciation of how this infection would manifest during pregnancy and the postpartum period could be achieved, and thus, the revised recommendations for medical countermeasures could be more broadly based. In particular, a determination of the risk-benefit profile of the medical therapies recommended for obstetrical populations, must take into account the course of the maternal illness and the risks of the infection for both the mother and offspring.

To date, minimal data has been published on anthrax during pregnancy and the postpartum period thus, the effects of anthrax on these potentially at-risk women and

their offspring is largely unknown. The largest study conducted was a systematic review published by Jamieson et al. in 2006, which identified five cases of anthrax reported during pregnancy (Jamieson, Ellis et al., 2006). The small number of cases limited the conclusions that could be drawn in the review but major knowledge gaps were identified. Notably, it remained unclear whether the physiologic changes during pregnancy and the postpartum period would affect a woman's susceptibility to anthrax or the severity of a *B. anthracis* infection. In addition, it was unknown whether perinatal transmission of the organism was possible during pregnancy, birth or breastfeeding.

In efforts to provide a better understanding of the natural history of anthrax in pregnant and postpartum women, a systematic review of the worldwide literature was conducted focused on the following five questions:.

1) Are pregnant and postpartum women more or less susceptible to *B. anthracis* than the general population?
2) Is *B. anthracis* infection more severe in pregnant and postpartum women than in the general population?
3) Is there an increased risk of adverse obstetrical outcomes in women infected with *B. anthracis*?
4) Is there a risk of congenital infection in infants whose mothers are infected with *B. anthracis*?
5) Is there a risk of *B. anthracis* transmission through breast milk?

Chapter II. - Literature Review

Bacillus anthracis is categorized by the CDC as a Category A bioterrorist agent, which specifies it as a high priority agent that poses a risk to national security (Wright et al., 2010) Category A agents are defined by the following characteristics 1) can be easily disseminated or transmitted from person to person; 2) result in high mortality rates and have a potential for a major public health impact; 3) might cause public panic and social disruption; and 4) require special action for public health preparedness. (CDC, 2012)

Although it has been 11 years since the anthrax bioterrorist attack, the interest in anthrax as a biological threat has not waned. In 2008, the Secretary of the Department of Homeland Security deemed that there is a still significant potential for a biological attack with *Bacillus anthracis*. This resulted in a declaration, issued by the Secretary of Health and Human Services in October 2008, allowing for the emergency use of in-home kits for post-exposure prophylaxis (Lutter, 2008). In July 2011, this declaration was renewed, indicating that anthrax is still a national concern (DHHS 2011). Furthermore, in a September 2011 Institute of Medicine (IOM) report, commissioned by the Office of the Assistant Secretary for Preparedness and Response (ASPR), anthrax was described as "one of the most serious threats to national security and the health of the nation"(IOM, 2011).

The IOM estimates that at least 13 countries may have offensive biological

weapons programs and in fact, some terrorist groups have already attempted to weaponize anthrax. (Kerr et al., 2008; Ingelsby et al., 2002, Wright et al., 2010; IOM, 2011). One specific example was the Aum Shinrikyo, a Japanese cult that released anthrax throughout Tokyo multiple times in 1995. Fortunately, no illnesses resulted from these intentional releases because the anthrax strain released was an innocuous one (Inglesby et al., 2002).

Additionally, there have been unconfirmed reports of Al Queda possessing *B. anthracis* as part of a bioweapons program (Inglesby et al., 2002; Mowatt-Larssen, 2010), and Iraq has been reported to have tested mechanisms to aerosolize anthrax. (Inglesby et al., 2002; Wright et al., 2010). Additionally, in 1979, an anthrax epidemic in animals and humans was discovered in Svedlosk, a city within the Soviet Union. This was linked to the windborne spread of an aerosolized anthrax pathogen accidentally released from a military facility. As a result, 96 cases of *B. anthracis* infection occurred, resulting in 64 deaths (Meselson et al., 1994; Wright et al., 2010). This demonstrated that anthrax had the potential to be used as a bioweapon (Meselson et al., 1994). Previously, the United States had also investigated anthrax as a potential weapon, conducting military trials in the 1960's. However, this program, along with all bioweapons research, was terminated by President Nixon's executive order in 1970 (Inglesby et al., 2002; Wright et al., 2010).

Over 30 years later, the United States experienced a relatively confined anthrax attack, during which approximately 10,000 people were presumed exposed and were offered prophylactic antibiotics post-exposure. (Shepard et al., 2002). As a result of a rapid public health response and confined exposures, only 22 people became ill. However, the threat of a much larger attack has been considered and would require a

significant greater response from the USPHS, CDC and the other federal agencies (Inglesby et al., 2002). World Health Organization experts estimate that the release of 50 kg of *B. anthracis* could result in 95,000 deaths and 125,000 hospitalizations. (WHO, 2010). In addition, the US Congressional Office Technology Assessment estimates that the release of 100 kg could result in between 130,000 and 3 million deaths (Office of Technology Assessment, 1993). With these estimates, it is critical that the nation be as prepared as possible and that medical countermeasures are mapped out before an event, and especially for pregnant and postpartum women.

Although the actual number of pregnant and postpartum women who were exposed to anthrax during the 2001 attack is unknown, there were no clinical anthrax cases among these women. However, 2% of the 2,444 women who received prophylaxis did report being pregnant or having been pregnant while taking the recommended antimicrobials (Shepard et al., 2002). This fact alone argues that pregnant women have already potentially been exposed to *B. anthracis* and emphasizes the importance of studying anthrax, as well as medical countermeasures in this population. With an estimated 4.1 million live births yearly in the United States, and the large number of illnesses and casualties anticipated in a large scale anthrax attack, a substantial number of pregnant or postpartum women could be affected. (Ventura et al., 2009; Hamilton et al., 2010)

A thorough review of the 96 cases of anthrax in the Soviet Svedlosk incident failed to identify any cases among pregnant or even postpartum women (Meselson et al., 1994). In addition, none of the 10,000 anthrax cases diagnosed in a 1980s Zimbabwe epidemic were reported as pregnant or recently pregnant women (Davies, 1982; Davies,

1982; Mwenye at al., 1996). There have also been recent reports in the past five years of naturally-occurring anthrax involving gastrointestinal, inhalation and injection anthrax, and none of these were individuals were pregnant or postpartum (MMWR, 2006; Walsh et al., 2007, Booth et al., 2010). Given that bioterrorist-induced anthrax during pregnancy or the postpartum period has not been reported (Messelson et al., 1994; MMWR, 2001), heretofore the little knowledge that was known about anthrax in obstetrical populations was derived from five naturally-occurring cases (Jamieson, Ellis et al., 2006). As the CDC develops new anthrax recommendations with special provisions for pregnant and postpartum women, it is critical that the public health community draw upon all the possible evidence to determine the unique issues of this group. As such, the main impetus behind this systematic review was to uncover as much data as possible regarding anthrax in the pregnancy period to better inform policymakers and health care providers to allow for informed decision-making in the event of an anthrax attack.

B. anthracis is a zoonotic disease caused by a facultative anaerobic, gram-positive, spore-forming bacterium which is found naturally in the soil (Dixon et al., 1999; Inglesby et al., 2002 Wright et al., 2010). Herbivores, such as horse, sheep and goats are the natural hosts of anthrax, becoming infected through the ingestion of spores in the soil (Inglesby et al., 2002; Wright et al., 2010). Estimating the worldwide incidence of naturally-occurring anthrax infection in animals is difficult because of unreliable reporting but certain countries, such as Iran and Turkey continue to report anthrax regularly (Doganay & Metan et al 2009, Wright et al., 2010). However, with the advent of effective animal vaccination programs, livestock infection has become extremely uncommon in the United States (Inglesby et al.,2002), but outbreaks sporadically

occur in the Great Plains states (Wright et al., 2010).

One of the most unique, yet most dangerous aspects of *B. anthracis* is that the organism exists in 2 forms, a vegetative and a spore form. The spore form is very resistant to heat, cold, drought, disinfectants, ultraviolet light and gamma radiation and can survive for long periods of time in the environment, perhaps even decades (Wright et al., 2010). The spore form is a "resting state' that germinates into the vegetative form in nutrient-rich locations, such as the blood or body tissues of animals or humans (Inglesby et al., 2002). As a natural infection, humans can acquire *B. anthracis* infection from contact with infected animals or animal products, and can ingest or inhale anthrax spores which subsequently germinate to cause infection. Most of what is known about these infections is derived from naturally-occurring cases and the case fatality rate has ranged from <1%, for cutaneous anthrax that was appropriately treated, to 89%, for inhalational anthrax. Over 95% of anthrax reported worldwide has been cutaneous infections, however, inhalational and gastrointestinal anthrax have been reported and cause much more serious infections (Ingelsby et al., 2002; Doganay & Metan, 2009; Doganay et al., 2010; Wright et al., 2010).

Human inhalational anthrax is the most concerning form of the disease, particularly in the setting of a bioterrorist event. In this form, the infection has between a 45% and 89% case fatality rate and requires prompt diagnosis and treatment to achieve survival (Holty et al., 2006; Walsh et al., 2007; Wright et al., 2010). The route of exposure is the inhalation of spores which lodge in the respiratory tract and, can either germinate causing severe respiratory compromise, or can remain dormant for months and

cause an infection at a later time (Holty et al., 2006; Wright et al., 2010). Once inhaled, the spores are transported to the pulmonary lymph nodes where the organisms proliferate, and release toxins that enter the bloodstream. Severe systemic disease may result which often results in death (Inglesby 2002, Wright 2010). Inhalational anthrax has a bisphasic course, with the initial illness followed by a brief period of recovery, and then a rapid decline in fulminant phase, characterized by respiratory distress, shock and death (Ingelsby 2002, Holty 2006). The initial phase can last 1- 6 days with a typical fulminant phase of less than 24 hours, after which there are few survivors (Holty et al., 2006).

Key features of inhalational anthrax make the bacteria an attractive biological agent of war; 1) the inhalational form can progress from exposure to severe illness very quickly, 2) the dormant spores are resistant to antimicrobial treatment, and 3) the spores are difficult to detect (Wright et al., 2010). As mentioned, dormant spores can live in the human host for extended periods of time and can unpredictably germinate and cause severe disease. The estimated timeframe from dormancy to germination predicted in non-human primate models is up to 60 days post-exposure, but has been show to be even longer in some animal models (Friedlander et al., 1993). The World Health Organization and the Office of Technology Assessment predicted that widespread morbidity and mortality would result from the release of aerosolized *B.anthracis* and deaths that would primarily be in the form of inhalational anthrax (Office, 1993;WHO, 2010).

Much of the information regarding inhalational anthrax is derived from 82 cases that were reported in a systematic review of the literature from 1900-2005, which included the 11 bioterrorism cases in the United States (Holty et al., 2006). In addition, there were two recent cases of naturally-acquired inhalational anthrax, which appeared to result from natural exposure to animals and animal hides (MMWR, 2006; Walsh, 2007). Survival from inhalational anthrax seemed to improve with early use of multidrug antimicrobials, anthrax antiserum and aggressive

drainage of pleural fluid (MMWR, 2006; Walsh, 2007). In the 2001 inhalational cases, the mortality of among those infected was 45%, highlighting the continued threat this organism poses (Holty et al., 2006). More than any other form of anthrax, the experience with inhalational anthrax underscores the need to have a bioterrorism preparedness plans in place for the entire population, including pregnant and postpartum women. In the setting of a large scale aerosolized attack, clinicians and public health responders will need to respond quickly, diagnosing and treating anthrax before severe illness manifests. A systematic plan for post-exposure prophylaxis will also be central to the public health response. Clinicians and public health practitioners will rely heavily on CDC guidance during an anthrax event, thus highlighting the importance of the CDCs recent activities to ensure an appropriate plan is in place for all.

At present, there are no confirmed reports of inhalational anthrax among pregnant and postpartum women in the worldwide literature; the behavior of this form of anthrax in this "at-risk" population is largely unknown. It is uncertain if respiratory and systemic progression would be the same, less severe or more severe in pregnant and postpartum women and there are some physiologic changes during pregnancy and the postpartum period that raise concerns of the possibility of a worse case presentation of anthrax in this population. The increased plasma volume of pregnancy and the known respiratory changes; increased respiratory secretions, decreased pulmonary compliance, and maternal oxygen reserve (Weinber, 1984; James, 2005, Cono et al., 2006) may cause inhalational anthrax to portend a worse prognosis. Because these changes persist after delivery, postpartum women may also be at risk for more severe disease. Exploration of *B. anthracis* infection in the context of these physiologic changes of pregnancy would be important to determine if the infection is more severe, as has been observed with other infections. Other respiratory illnesses, such as influenza and varicella, have been demonstrated to be more severe in pregnancy (Jamieson, Theiler & Rasmussen, 2006). The unique physiology of

pregnant and postpartum women also contributes to immune shifts during pregnancy, which may alter the immune response to B. anthracis and could also contribute to greater morbidity and mortality.

Another question that arises regarding inhalational anthrax in pregnant women is whether they are more susceptible to developing infection. Pregnancy is known to induce immune tolerance, which is necessary to prevent maternal rejection of fetal tissue (Weinberg, 1984). Immune changes include a shift from a T helper 1 to T helper 2 predominance, resulting in a shift away from cell-mediated immunity and toward humoral or antibody-mediated immunity (Jamieson , Theiler & Rasmussen, 2006). Although bacterial infections are more heavily dependent on an intact humoral response, it is unknown if these immune shifts contribute a heightened susceptibility to certain bacteria. It is has been shown that with other bacterial infections, such as plague and Salmonella, the risk of infection has been demonstrated to be increased during pregnancy (Weinberg, 1984, Samuel & Barry, 1998)

The questions of the susceptibility and severity of anthrax are valid concerns and have been raised by the public health community previously in relation to emerging infectious diseases in pregnancy (Rasmussen & Hayes 2005). Since it is unlikely that a cohort of pregnant women with naturally-occurring anthrax could be monitored prospectively, and since animal models currently do not exist, it is critical that all previous cases of anthrax be collected and analyzed to uncover any pertinent trends. This may lead to the greater understanding of the severity and susceptibility of pregnant women and postpartum women to anthrax. At present, retrospective data appears to be the only way to access more information to inform bioterrorism response plans. Furthermore, given the high mortality of inhalational anthrax, future cases may not survive long enough to provide a clear clinical picture in pregnant women. Instead, historic cases of anthrax, and more likely a preponderance of cutaneous cases, will be relied upon to inform the new pregnancy guidelines.

Cutaneous disease would also be a concern in the event of a bioterrorist attack, as evidenced by the fact that 50% of the cases in the 2001 attacks were this form of the infection. Based on previous data in the general population, this form of anthrax has a less aggressive course and a lower mortality rate than inhalational anthrax (Celia, 2002; Doganay & Metan, 2009; Doganay et al., 2010). Cutaneous anthrax is the most common form reported worldwide , with estimates of approximately 2000 cases annually worldwide (Ingelsby et al., 2002; Wright et al., 2010; Doganay et al., 2010). The human cutaneous form is contracted from contact with infected animals or contaminated animal products. Denuded or abraded skin is particularly susceptible to the entry of anthrax spores and areas of greatest exposure, such as the face, neck, arms and hands are most often affected. Once the spores enter the body, they germinate and release toxins similar to the effects in inhalational anthrax. Toxin effects cause significant edema, skin necrosis and painful enlarged lymph nodes (Dixon et al., 1999; Ingelsby et al., 2002; Wright et al., 2010). The appearance of cutaneous anthrax is very characteristic; painless, firmly adherent, black eschar over the surface of an ulcer. A very astute clinician with a high suspicion for the disease can make the diagnosis clinically, but lesions can also be easily confused with other causes such as a spider bite, staphylococcal or streptococcal cellulitis and herpes, all of which are much more common diagnoses (Dixon et al., 1999; Celia, 200; Inglesby et al., 2002; Doganay & Metan, 2009; Doganay et al., 2010).

Developing countries represent the greatest burden of cutaneous anthrax with the largest epidemic seen in Zimbabwe in the 1980's whereby over 10,000 cases were reported (Mwenye, 1996; Davies, 1982; Davies, 1982). Although the case-fatality rate for appropriately treated cutaneous anthrax is only 1% (Doganay et al., 2010;Wright et al.,2010), a 10-40% mortality rate has been reported in untreated cases (Dogany et al., 2010, Ingelsby et al., 2002). The average time between exposure and the incidence of cutaneous disease is generally considered 5-7 days, although in the Svedlosk incident , cases of delayed anthrax did occur 13 days after exposure

(Messelson et al., 1994; Wright et al., 2010). In the 2001 event, there were 11 people diagnosed with confirmed or probable cutaneous anthrax and of those, all were estimated to have been exposed within a 10 day time frame and none of the cases were fatal (MMWR, 2001).

The third form of disease caused by *B. anthracis* is gastrointestinal anthrax, which is a rare form of the disease worldwide (Doganay & Metan, 2009), but particularly rare in the United States (MMWR, 2006). Gastrointestinal illness develops after the ingestion of contaminated meat containing large numbers of vegetative bacilli that improper cooking methods have failed to destroy. Individuals with gastrointestinal anthrax are often gravely ill, with most developing systemic illness in conjunction with their gastrointestinal symptoms. Albeit rare, this form of the disease has significant mortality rate, ranging from 25-60%, which is partially attributable to the difficulty in making the diagnosis (Lew, 1995; Inglesby et al., 2002). Of note, there were no cases of gastrointestinal cases in the Svedlovsk or 2001 anthrax events, but there has been a recent report of naturally-occurring gastrointestinal anthrax reported in the United States in 2009 (Inglesby et al., 2002; MMWR 2010).

Physiologic changes occur in the gastrointestinal tract of pregnant and postpartum females; delayed gastric emptying, decreased gastrointestinal motility, decreased gastrointestinal blood flow and lower gastric acidity are among the known changes (Cono et al., 2006), but how these relate to anthrax infection is yet unclear. Although the impact of these changes, in terms of susceptibility to or severity of anthrax cannot be answered, there are some theoretical concerns. Delayed gastric emptying and lower gastric acidity may heighten susceptibility to anthrax by allowing it to replicate more readily in the gastrointestinal tract. Slower gastrointestinal transit times could also allow the accumulation of vegetative *B anthracis* and cause more damage to the gastrointestinal mucosa, perhaps resulting in a greater risk of systematic disease. There is already evidence that pregnant women may be more susceptible to gastrointestinal infections of other

types and therefore this may be relevant in gastrointestinal anthrax during pregnancy as well (Samuel & Barry, 1998).

Another rare form of anthrax was recently reported in Scotland, whereby 31 intravenous drug abusers were found to have anthrax in their tissues. The route of exposure was mapped to the area of heroin injection, and many of these patients developed severe illness resulting in 11 deaths. Although the exact origin of anthrax infection among this group is unknown, it is suspected based on the distribution of cases that the heroin was naturally contaminated, and that bioterrorism was not a concern (Booth et al., 2010). Given that this form is unlikely to result from intentional release of the agent, the revised CDC guidance on bioterrorism, will unlikely address it.

Much of the knowledge regarding anthrax infection in the general population stems from three sources, naturally occurring cases, the Svedlosk incident, and the 2001 bioterrorist attacks. Among all these sources, only five cases of *B. anthracis* infection have been previously identified in pregnant or postpartum women, and none have been in association with a bioterrorist event or even an inhalational form of the infection. As plans for a public health response to an anthrax attack evolve and undergo evidence-based revisions, it is important that any and all information pertaining to anthrax in pregnant and postpartum women be gathered and evaluated. The primary aim of this systematic review is to collect all the reported anthrax cases in pregnancy and the postpartum period to provide a review of the evidence to better inform the new recommendations.

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Chapter III. - Manuscript

A Systematic Review of Anthrax Cases in Pregnant and Postpartum Women

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Precis

Based on 19 cases reported in the world's literature (16 among pregnant and 3 among postpartum women), *Bacillus anthracis* infections in pregnant and postpartum women portend a poor prognosis and maternal-fetal transmission may occur.

Abstract

Objective: To describe the worldwide experience of *Bacillus anthracis* infection reported in pregnant and postpartum women.

Data Sources: Studies were identified through MEDLINE, WEB OF SCIENCE, EMBASE, and GLOBAL HEALTH databases from inception until April 2012. The keywords [("anthrax" or "anthracis") and ("pregna*" or "matern*" or "post partum" or "postpartum" or "puerperal" or "lact*" or "breastfed*" or "fetal" or "fetus" or "neonate" or "newborn" or "abort*" or "uterus")] were used. In addition, all references from selected articles were reviewed, hand searches were conducted and relevant authors were contacted.

Methods of Study Selection: The inclusion criteria were: 1) published articles referring to women diagnosed with an anthrax infection during pregnancy or within six months postpartum, 2) any article type reporting patient-specific data, 3) articles in any language, and 4) non-duplicate cases. Non-English articles were professionally translated. Duplicate reports, unpublished reports and review articles depicting previously identified cases were excluded.

Tabulation, Integration and Results: Two authors independently reviewed articles for inclusion. The primary search of the 4 databases yielded 800 articles and the secondary cross-reference search revealed 146 articles. Seven articles from these searches met inclusion criteria. By contacting the lead author of the largest systematic review of inhalation anthrax to date, 6 additional articles, published before the databases' inception,

were identified that met inclusion criteria. In total, 19 cases of anthrax infection were found, 16 in pregnant women and 3 in postpartum women.

Conclusions: Based on these case reports, anthrax infection in pregnant and postpartum women is associated with high rates of maternal and fetal death. Evidence of possible maternal-fetal transmission of *B. anthracis* was identified in early case reports. Transmission of *B. anthracis* through breast milk has not been reported. This review provides important insight to guide anthrax treatment and prophylaxis recommendations for pregnant and postpartum women.

Introduction

In 2001, the United States experienced a bioterrorist attack involving *Bacillus anthracis* spores disseminated via the postal system. As a result, twenty-two people became infected with anthrax, of which five people died from inhalation anthrax, the most deadly form of the disease (IOM 2011). In addition, approximately 10,000 people were offered antibiotic prophylaxis (Shepard 2002). Although it has been eleven years since the anthrax attack, concern about anthrax as a biological threat remains. As recently as 2011, the Secretary of the Department of Homeland Security issued a declaration indicating that anthrax is still a national concern (Lutter 2008, DHHS 2011). A September 2011 Institute of Medicine (IOM) report describes anthrax as "one of the most serious threats to national security and the health of the nation" and estimated offensive biological weapons programs were present in up to twelve countries during the past two decades. Some terrorist groups have already attempted to use anthrax as a bioweapon (IOM 2011).

Because pregnant women and their offspring may be at increased risk for complications from certain infections (Rasmussen 2005), and because there may be concerns about the safety of treatment and prophylaxis strategies among pregnant and lactating women (Cono 2006), it is critical to carefully consider how these women may be affected in an anthrax event. In addition, during the 2009 H1N1 pandemic, it was noted that the increased risk of influenza-associated complications extended to the postpartum period (Louie 2011). Given that there are nearly 7 million pregnancies and more than 4 million births in the United States per year, a large scale anthrax attack would likely affect a substantial number of pregnant and postpartum women (Ventura 2009).

This systematic review examines the worldwide scientific literature to synthesize the knowledge of anthrax during pregnancy and the postpartum period and addresses the following questions:

1) Are pregnant and postpartum women more or less susceptible to *B. anthracis* infection than the general population?
2) Is *B. anthracis* infection more severe in pregnant and postpartum women than in the general population?
3) Is there an increased risk of adverse obstetrical outcomes in pregnant women infected with *B. anthracis*?
4) Is there a risk of congenital infection in infants whose mothers are infected with *B. anthracis*?
5) Is there a risk of *B. anthracis* transmission through breast milk?

Sources

We searched the following databases: PUBMED, WEB OF SCIENCE, EMBASE and GLOBAL HEALTH, from inception to April 2012, to identify all listed publications in the medical literature discussing anthrax in pregnant and postpartum women using the following search terms: [("anthrax" or "anthracis") and ("pregna*" or "matern*" or "postpartum" or "post partum "or "puerperal" or "lact*" or "breastfed*" or "fetal"or "fetus" or "neonate" or "newborn" or "abort*" or "uterus")]. For this review, we placed no restrictions on the language of publication and defined postpartum women as women who have given birth in the last 6 months. Additionally, we examined the bibliographies of all selected articles to identify additional references and we conducted a hand search of

the personal files of a CDC subject matter expert (DJJ). Lastly, we contacted the lead author of the largest systematic review of inhalation anthrax (Holty 2006) and other relevant systematic anthrax literature reviews, to identify additional articles pertaining to pregnant or postpartum women.

Study Selection:

The inclusion criteria were: 1) published articles referring to women diagnosed with an anthrax infection during pregnancy or within six months postpartum, 2) any article type reporting patient-specific data, 3) articles in any language, and 4) non-duplicate cases.

One reviewer (DMD) screened all the titles, relevant abstracts and articles identified by the search strategy and selected those containing clinical data on anthrax in pregnant or postpartum women. When the abstract included such clinical information, or the abstract was not available, a full text review of the paper was conducted. Any paper describing a case of anthrax during pregnancy or the postpartum period was analyzed, including published case reports, case series and review articles, but to meet our inclusion criteria, a primary published report was required. No case-control or cohort studies were available and policy and practice articles were excluded from the review. Relevant non-English articles were professionally translated. A second reviewer (DJJ) read and reviewed all selected articles. CDC experts in anthrax, emerging infectious diseases, emergency preparedness and pediatrics reviewed the manuscript and the cited references to ensure accuracy and completeness.

Data elements extracted from the articles included: 1) age of the woman; 2) geographic location; 3) anthrax clinical presentation; 4) gestational age at illness onset or time from

delivery; 5) method of diagnosis; 6) treatment, 7) obstetrical outcome, 8) neonatal outcome and 9) autopsy findings. In addition, any information pertaining to the diagnosis of anthrax in the fetus or neonate was carefully reviewed and recorded.

Tabulation, Integration and Results

Database searches identified 800 articles, of which seven met the inclusion criteria (Figure 1). All seven were extracted from the PUBMED database search. Review of the 146 references cited in these 7 articles and hand-searches failed to identify any additional articles. Review of the references in the largest systematic review of inhalation anthrax published to date also failed to identify additional articles. However, personal communication with the lead author of the systematic review of inhalation anthrax yielded one additional case report from Germany (Regan 1923). Through this case report, 6 additional non-English articles were identified which predated the inception of the four databases queried (Morisani 1886, Paltauf 1888, Romano 1888, Eppinger 1888, Rostowzen 1897, Vogt 1927). Overall, 13 papers reported clinical information describing 19 cases, 16 in pregnant women and 3 in postpartum women (Kohout 1964, Daneshbod 1970, Sujatha 2002, Tomasiewicz 1988, Handjani 1976, Dutz 1971).

Case duplication and primary report status were assessed. Reports of cases from the same geographical location during the same time period were specifically evaluated. Only one case was felt to overlap by both reviewers (Kohout 1964) and the case was only included once. One additional case of anthrax in a pregnant woman was referenced in the medical

literature, for which we were unable to identify a confirmatory primary report (Cantoni, as cited in Romano 1888).

We evaluated the geographic and temporal distribution of the cases (Table 1). Of the 19 cases reported in pregnant and postpartum women, only one case was reported in the United States, a case from 1923 in New York (Regan 1923). The location of the other cases included: Turkey, India, Poland, Iran, Italy and Germany, which reported the greatest number of cases (n=5). The timeframe of the case reports ranged from as early as 1886 through 2003. All of the pregnant women reported were in the 2nd or 3rd trimester when they were diagnosed with anthrax, with an approximate average age of 32 years and an average gestational age of 31 weeks.

We tabulated the site and form of *B. anthracis* infection, as well as the exposure mechanism (Table 1). All of the cases reported in this review were naturally-occurring anthrax and of these, 13 were cutaneous anthrax, 2 were gastrointestinal anthrax, 1 was a uterine infection related to an attempted abortion and 3 were presumed inhalational infection. Of the cutaneous cases, most involved the face (n=11), and 2 involved the extremities. Contact with infected animals (n=2), wool sorting (n=3) and ingestion of meat (n=3) were identified as potential sources of exposure.

Obstetrical outcomes were analyzed. Of the 19 cases of anthrax infection reviewed, 15 resulted in maternal deaths, representing a maternal case fatality proportion of 79%. Two of these maternal deaths were in postpartum women who had delivered 3 days prior to presentation. When the cases were stratified by anthrax form, 69% of cutaneous, 100% of gastrointestinal and 100% of uterine cases resulted in maternal death. In addition, the

three cases of suspected inhalation anthrax also resulted in maternal fatalities. Regarding fetal outcomes, 5 of the 15 pregnant women delivered live born infants, 10 fetal deaths were reported, all in association with maternal deaths, and the neonatal outcome was not reported in one case. No congenital anomalies were reported in any of the surviving neonates. Preterm labor was noted in 3 cutaneous anthrax cases with an average gestational age at delivery of 34 weeks, ranging from 7-21 days after hospitalization for the infection. Labor was coincident with the infection in three additional full term cases.

The clinical presentation of cutaneous anthrax involved the appearance of necrotic tissue or "malignant pustules" often with significant surrounding edema. Both cases of gastrointestinal anthrax presented with abdominal pain, but in one case, it was misdiagnosed as a ruptured ovarian cyst, with anthrax bacilli only discovered at autopsy (Handjani 1976). The 3 presumed cases of inhalation anthrax were all based on autopsy results, therefore clinical presentation data was not available. *Bacillus anthracis* was demonstrated in 8 cases by peripheral smear (Kadalani, 2003 Sujatha 2002, Tomasiewz, 1998 Handjani 1976, Kohout, 1964 Reagan 1923, Vogt 1927, Morisani 1886); in 10 cases the organism was identified within tissues at autopsy (Handjani 1976, Dutz 1971, Daneshbod 1970, Rostowzew 1897, Eppinger 1888, Paltauf 1888), and in 1 case the diagnosis was made clinically, without laboratory testing (Romano 1888).

Management of cases varied over time. Antibiotics were used in the treatment of anthrax infection in cases reported in 1964 or later, with penicillin as the most commonly reported antibiotic. Interestingly, 3 of the 4 women who survived cutaneous anthrax were treated with penicillin. (Kadalani 2003, Tomasiewicz 1998, Vogt 1927) Other were

antibiotics used for treatment of included cefotaxime, streptomycin and clindamycin. In the cases reported before 1964 (1886, 1888, and 1923), surgical debridement and cautery were described as part of the treatment. Anthrax antiserum was used as part of the management in one case reported in 1923. (Reagan 1923)

B. anthracis was identified in fetal tissues in 5 cases of maternal cutaneous infection. The first 3 of these cases were all reported by the same author in Germany in 1897(Rostowzen 1897). The fourth case was documented by a second German author in 1888 (Paltauf 1888), and the last case by an American author in 1923 (Reagan 1923). These reports indicate the presence of anthrax bacilli in the uterus, placenta, amniotic fluid and fetal tissues, including the fetal lung, heart, liver, spleen, kidneys and adrenal glands. One case reported the highest number of bacilli in the fetal liver, with bacilli in even greater quantities than the amount present in the maternal liver. However, in another 3 cases resulting in fetal deaths, autopsies were performed and failed to demonstrate evidence of fetal infection (Eppinger 1888, Romano 1888). No reports, for which information is available, indicate neonatal infection in the surviving neonates. Maternal-to-infant transmission of anthrax via breast milk was not demonstrated in the one case report of a postpartum woman diagnosed with cutaneous anthrax who breastfeed (Vogt 1927). Of note, this woman's lesion was restricted to her hand and no lesions were present on or near her breasts.

Discussion:

This review summarizes the worldwide literature of anthrax during pregnancy and the postpartum period and provides some insight into the natural history of the disease in

these women. Our review highlights the limited information available regarding anthrax infection and its management in pregnant and postpartum women. This makes it difficult to determine the ideal treatment and prophylaxis regimens for these women. In particular, there were 3 cases of possible inhalation anthrax in pregnant women, but these could not be confirmed with clinical data. This poses a challenge to our understanding of this form of the disease, which is likely to occur a result of a bioterrorist attack. On the other hand, cutaneous anthrax, often resulting from exposure to sick animals or animal products is most represented in this review, which is consistent with this form being the most common clinical presentation of naturally-occurring anthrax in the general population (CDC website, Inglesby 2002). Lastly, there were only two pregnancy-associated cases of gastrointestinal anthrax identified in the reports reviewed, thus making in difficult to draw conclusions regarding this form of the disease.

The aim of this article was to address 5 specific issues related to anthrax infection during pregnancy and the postpartum period: 1) susceptibility, 2) severity, 3) obstetric outcomes, 4) congenital infection, and 5) transmission through breast milk. The first question relates to the susceptibility of pregnant and postpartum women to anthrax infection. The small number of cases we identified through an extensive and systematic search limits our ability to answer this question. It may be that pregnant and postpartum women are less likely to develop anthrax infection. However, it is not possible to determine if pregnant and postpartum women are less susceptible to anthrax or whether they are simply less frequently exposed. In addition, there may be reporting bias, in which cases among pregnant and postpartum women are more or less likely to be

reported. Another explanation may be that cases reported in the literature do not accurately capture pregnancy status. Therefore, we are not able to conclude whether pregnant women are more or less susceptible to anthrax than the general population, but certainly pregnant and postpartum women can develop *B. anthracis* infections.

Our second question dealt with the severity of infection. We found that maternal deaths have been reported in association with anthrax disease, with fairly high death fatality ratios for cutaneous anthrax. The number of fatalities reported in this review is much higher than the previously reported mortality rate for cutaneous anthrax in the general population, which ranges from 1% for antibiotic-treated infections (Inglesby 2002) to 10-40% for untreated infections (Doganay 2002, Inglesby 2002). In addition, the two gastrointestinal cases of maternal anthrax and the three presumed cases of inhalation anthrax were fatal as well. Although certain infections may be more severe during pregnancy and the postpartum period (Jamieson 2006, Mosby 2011), with these small numbers, it is not possible to ascertain whether anthrax infections are more severe among pregnant and postpartum women than the general population. Without larger numbers of patients and more outcome data from appropriately treated pregnant and postpartum women, one cannot discern if the disease is more severe.

Several factors may explain the high number of maternal deaths that we observed. First, in some cases, delays in seeking medical care, making the correct diagnosis, and instituting effective treatment may have contributed to poor outcomes. In at least one case, anthrax was misdiagnosed as a ruptured ovarian cyst leading to a surgical exploration and delayed treatment (Dutz 1971), which may have impacted the severity of the illness. Second, the timeframe of the reports includes pre-and post-antibiotic eras,

with pre-antibiotic cases contributing 7 of the 13 deaths among pregnant women and the issue of timing and appropriateness of antibiotics could not be assessed. Most women did not receive multi-agent antibiotic therapy, the current standard of care for treatment of serious anthrax infections (Stern 2008). Even though clear evidence of disease severity in pregnant and postpartum women receiving appropriate treatment is lacking, it is prudent to assume that *B. anthracis* infection poses at least the same risk as that for the general population. Thus, if a bioterrorist attack with anthrax were to occur, treatments should be no less aggressive for pregnant and postpartum women than for the general population.

In terms of the risks of adverse obstetrical outcomes among women infected with anthrax, three pregnant women with cutaneous anthrax developed preterm labor (Kadanali 2003, Tomasiewicz) and labor was coincident with the infection in 3 additional cases (Kohout 1964, Daneshbod 1970). These cases raise the question of whether anthrax infection may be a factor in promoting the onset of labor, a finding that has been described in other severe infectious processes (Louie 2011, Jamieson 2006, Cono 2006, Yost 2000). It would be important to establish if this observation is a consequence of the release of inflammatory mediators, or if there are certain pathogenic characteristics to *B. anthracis* that stimulate uterine contractions. Given the rapid deterioration documented in severe anthrax infections, it may be difficult to determine the exact mechanism by which anthrax impacts pregnancy outcome. (Kadalani 2003).

Regarding the risk of congenital infection, 5 cases reported evidence of *B. anthracis* in the fetal tissues at autopsy (Paltauf 1888, Rostowzen 1897, Regan 1923). Given that these reports were published in 1888, 1897 and 1923, it is impossible to determine the

accuracy of this information. Nonetheless, these 5 reports, as well as the 10 fetal deaths reported in association with maternal anthrax infection, indicate that the possibility of congenital infection cannot be excluded. Anthrax bacilli have been identified in the placenta, within the chorionic villi and the amniotic fluid, and also within the umbilical vessels. The organism has been identified in the fetal lung, heart, spleen, adrenals and liver, with the greatest concentration documented in the fetal liver (Rostowzew 1897). Since techniques for conducting fetal autopsy have certainly evolved since 1923, the year of the latest report of fetal anthrax, it is difficult to know if these cases could represent contamination, rather than true infection, however the preventive measures reported should have been sufficient to preclude contamination of fetal tissues (Regan 1923). Although 3 of the 5 cases were reported by the same author in Germany (Rostowzen 1897), 2 other authors have identified anthrax in fetal tissues, including one in the United States (Regan 1923, Paltauf 1897). These findings do warrant the consideration of the possibility of vertical transmission of anthrax, and, congenital infection has been reported in animal studies (Strauss and Chamberland, 1882, as cited in Regan 1923).

Of note, no congenital anomalies were reported in the live born infants delivered by women with anthrax infection and no reports document congenital infections among these infants. However, none of the surviving infants had mothers who were exposed in the first trimester, the most critical time period for organogenesis. Ultimately, if maternal-fetal transmission is considered a possibility, then treatment choices may need to include antibiotics with known transplacental passage. Although this issue requires further study, perhaps using animal models, future recommendations for antibiotic treatment and prophylaxis for pregnant women may need to take this into account.

Finally, regarding the risk of transmission through breastmilk, only one case report was identified in a postpartum woman known to be breastfeeding while being treated for an anthrax infection. In this instance, the continuation of breast feeding during the infection did not result in neonatal anthrax (Vogt 1927). Of note, in this case, the cutaneous anthrax lesion was not in close proximity to the breast. Both the location of the cutaneous lesion and the milder form of the disease may be important factors to consider when interpreting the applicability of this case to the larger question of possible breast milk transmission. Thus, at present there is no evidence that *B anthracis* is transmitted in this manner in humans; however there have been rare instances reported where anthrax bacilli have been detected in the milk of a clinically affected infected dairy cattle (WHO 2008). Caution may need to be exercised in the case of cutaneous lesions affecting the breast or in the case of illness with severe non-cutaneous anthrax.

This systematic review has several limitations. First, despite an extensive search, this review may not have captured all of the cases worldwide of anthrax infection in pregnant and postpartum women. It may be that only the most severe cases are reported, falsely increasing the rates of maternal and fetal complications. Second, there are a small number of cases identified overall and many have limited clinical information. This substantially limits our ability to draw conclusions from these cases but does represent the largest collection of reports of *B. anthracis* infection in this population to date. Third, some of the data are retrieved from very old publications and different methods were used for evaluation and treatment of anthrax than are being used in the present day. Thus, maternal and fetal survival in the advent of newer antibiotics and better diagnostic techniques may be substantially different. Lastly, in some of the cases, autopsy findings

were the only source of information, and therefore clinical presentation or disease course could not be determined. This review highlights the need for additional research regarding anthrax exposure, infection and management in pregnant and postpartum women. Additional data regarding the severity of infection, obstetrical outcomes and the risks of maternal-fetal/infant transmission will help guide recommendations for prophylaxis and treatment in the event of a bioterrorist attack. Given the rarity of this condition in its natural state, animal research models may be the only mechanism to answer some of these questions. For now, we suggest that women and their fetuses are at risk for untoward outcomes from anthrax and recommend treatment and prophylactic regimens that are at least as aggressive as that recommended for general population, including the use of antimicrobials and the anthrax vaccine.

Table I. Anthrax Cases in Pregnant and Postpartum Women

Author/Year/Location	Gestational Age at Presentation	Clinical Summary	Laboratory Documentation of Diagnosis	Pregnancy Outcome
Pregnant Women				
Kadanali (2003);Turkey	32 weeks	**Cutaneous** (submandible**); Suspected exposure**-flaying of a dead cow 7 days prior to symptom onset. **Presentation** –submandibular eschar with fluid-filled vesicles, facial, neck and upper thorax edema, compromising respiratory function, fever, elevated WBC; **Treatment** - Penicillin G x 10 days; Prednisolone x 10 days	Direct exam of vesicle fluid revealed large gram-positive bacilli; the bacteria isolated was identified as *B. anthracis*. Gram stain and cultures of blood negative	Infection resolved after 10 days of treatment. Preterm delivery 13 days after presentation (34 weeks). No evidence of congenital infection.
Kadanali (2003);Turkey	33 weeks	**Cutaneous** (elbow); **Presentation** - weeping open lesion on right elbow with surrounding edema and swelling, fever, elevated white blood cell count; **Treatment**- Procaine penicillin x 7 days	Direct exam of vesicle fluid revealed large gram-positive bacilli; the bacteria isolated was identified as *B. anthracis*. Gram stain and cultures of blood negative	Preterm delivery despite tocolysis 7 days after presentation (34 weeks); No evidence of congenital infection
Sujatha (2002); India	not reported	**Gastrointestinal**(peritoneum); **Suspected exposure** - ingestion of improperly cooked beef 4 days prior to symptom onset; **Presentation** - abdominal pain, vomiting, bloody diarrhea, abdominal distension, pallor, guarding; **Treatment** – Cefotaxime and metronidazole x 1 dose	"Microscopic exam and culture of the diagnostic peritoneal fluid and blood revealed *B. anthracis"*	Maternal death on day of presentation. Presumed fetal death.

Tomasiewicz (1998); Poland	31 weeks	**Cutaneous** (eyelid); **Suspected Exposure** – mechanical trauma while working on farm. **Presentation** - massive edema of left side of face, fever, and regional lymph nodes 3 days after the injury, black necrotic eschar surrounded by fluid-filled vesicles, elevated WBC; **Treatment** – Penicillin (dose and duration not recorded) without response--> Clindamycin x 3 weeks, debridement 2 weeks postpartum for frontal bone necrosis requiring skin transplant	*B. anthracis* confirmed on culture of eschar and vesicular fluid	Improvement in edema after "several "days. Preterm delivery 3 weeks after presentation (34 weeks); 3200 g healthy infant.
Dutz (1971); Iran	not reported	**Uterine**; **Suspected exposure** - attempted abortion with contaminated stick. **Presentation** - massive hemorrhagic endometritis and hemorrhagic ascites	Anthrax observed in uterine tissue. Autopsy findings – necrotic endometrium, massive parametritis and rupture of an infected ovary	Maternal death; fetal death
Handjani (1976); Iran	16-20 weeks	**Gastrointestinal** (intestinal); **Suspected exposure** - ingestion of spores **Presentation** - shock, abdominal pain, hypotension, edema of vulva/vagina, vaginal bleeding, ascites, ; **Treatment** - Penicillin and streptomycin	Gram stain revealed gram positive rod-shaped bacilli- "typical bacillus anthracis" in gastrointestinal ulcers, submucosa, vessels and vessel walls. " Bacillus anthracis in the sinusoids of vessels"	Exploratory laparotomy for suspected ovarian cyst.which revealed interstitial edema, bladder ecchymosis, broad ligament hematoma, peritoneal hemorrhage, colonic edema. Maternal death 11 hours after presentation, 8 hours after surgery. Fetal death noted at time of exploratory laparotomy.

Kohout(1964); Iran	9 months	**Cutaneous** (eyelid); **Suspected exposure** - wool sorting. **Presentation** - red papules with necrotic lesions, eyelid edema progressing to facial edema making respiration difficult, neck/thoracic edema requiring tracheostomy, "toxic" appearing; crystalline penicillin and procaine penicillin , levophed	Anthrax smear and culture reported "positive"	Spontaneous delivery en route to hospital, Maternal death 2 days after symptom onset. Healthy infant - no evidence of anthrax bacilli in uterus or uterine cultures
Regan (1923); US	5-6 months	**Cutaneous** (cheek); **Route of Exposure**- unknown. **Presentation** - painless papule -->gradually enlarged of 2 days--> neck and chest edema→Decreased respiration and difficulty swallowing by third day when she presented to her physician. On physical examination - 1.5cm papule with eschar , neck thorax, eyelid swelling; **Treatment** - Anthrax serum injected intravenously, intramuscularly and around the anthrax lesion, wet dressing applied with chloramin-T, a disinfectant.	Peripheral smear and tissue demonstrated large gram-positive bacilli, some in chains and some demonstrating a capsule . Cultures from the maternal tissues yielded dry-grayish white colonies with a "medusa head" appearance, with square-ended, gram positive, non-motile bacilli occurring singly and in chains; culture inoculation into rabbits resulted in death within 72 hours.	Maternal death 5days after initial symptom onset. Fetal death at presentation. Fetal infection demonstrated with edema and consolidation in the lungs; anthrax appearing bacilli noted in fetal liver. Peripheral smears showed same bacilli in the placenta. Cultures from heart liver and amniotic fluid of fetus demonstrated few anthrax colonies , the same organism identified in mother.
Rostowzew (1897); Germany	8 months	**Cutaneous** (cheek); **Presentation** - "malignant pustule"	"Anthrax bacilli" in maternal organs; clustering in some samples	Maternal death 3 days after onset of illness; Fetal death; Anthrax bacilli in placenta, endometrium and muscularis of the uterus; umbilical vein/artery, fetal liver -more numerous bacilli than in maternal liver

Rostowzew (1897); Germany	7 months	**Cutaneous** (cheek and lip); **Presentation** - "malignant pustule"	"Anthrax bacilli" in maternal organs demonstrated by staining	Maternal death 3 days after onset of illness; Fetal death; Moderate number of anthrax bacilli in uterus, small number of bacilli in placenta, some seen in chorionic villi, isolated anthrax bacilli in umbilical cord, vein and tissue; Anthrax bacilli in fetal liver, spleen ,kidneys, and adrenals
Rostowzew (1897); Germany	4 months	**Cutaneous** (lip); **Presentation** - "malignant pustule"	"Anthrax bacilli" in maternal organs with clustering. "Pure anthrax cultures"	Maternal death 5 days after onset of illness; Fetal death; Few bacilli in uterus, Large numbers of anthrax in placenta; in chorionic villi, few bacilli in fetal liver spleen and adrenals; anthrax in amniotic fluid
Eppinger (1888); Germany	not reported	Presumed inhalation anthrax or "wool sorters disease"	Autopsy: "anthrax bacilli in transudates and exudates"; "pure cultures of same bacilli" Innoculation of mice→ evidence of anthrax.	Maternal death; Fetal death. Found evidence of anthrax in uterus and uterine vessels but not in chorionic villi or fetal organs
Eppinger (1888); Germany	not reported	Presumed inhalation anthrax or "wool sorters' disease"	Autopsy: "anthrax bacilli in transudates and exudates"; "pure cultures of same bacilli" Innoculation of mice→ evidence of anthrax.	Maternal death; Fetal death. Found evidence of anthrax in uterus and uterine vessels but not in chorionic villi or fetal organs

Paltauf (1888); Germany	5 months	Presumed inhalation anthrax; "Rag anthrax" similar to "wool sorters' disease" **Suspected exposure** – contact with contaminated animal products in the form of "rags" in a paper mill; **Presentation** – unknown; **Treatment** – unknown	Bacilli identified at autopsy in "groups and piles". These were identical to the bacillus that causes "spleen-burn"-> German for anthrax. "Thread-like bacilli in bundles, with sharply contrasting end pieces"	Maternal death; Fetal death. Found evidence of anthrax in placenta (large amounts), fetal lungs and fetal heart
Romano (1888); Italy	"full term"	**Cutaneous** (face); **Suspected exposure** - contact with pustules on infected spouse. **Presentation**-"malignant pustule", blackish leathery circular scab on glabella with facial, neck, scalp and thorax edema, respiratory difficulty; **Treatment** - Incision, cautery, internal antiseptics, carbolic acid, mercury bichloride, davaine's potion (iodine+potassium iodide)	Clinical diagnosis based on same disease in multiple family members with illness after ingestion of meat	Maternal death 6 days after onset of illness; Spontaneous delivery 4 days into illness; Healthy infant with mild cyanosis at birth
Morisani (1886); Italy	"close to term"	**Cutaneous** (cheek); **Presentation** - "malignant pustule", hard, black eschar surrounded by gangrenous tissue", coma, face and neck "greatly swollen" and eyelids swollen shut; **Treatment** – cautery	Autopsy findings: "short, very large bacterial rods with enlarged ends";"characteristic bacilli" in edematous fluid and maternal blood--> Injected piece of eschar into mouse and died; "pure cultures revealed anthrax" Autopsy: anthrax bacilli in transudates and exudates; pure cultures of same bacilli. Innoculation of mice→ evidence of anthrax.	Maternal death 5 days after the onset of symptoms; Spontaneous delivery of dead fetus believed to be alive at initial presentation-->Fetal death associated with illness
Postpartum Women				
Danesbod (1970); Iran	"term"	**Cutaneous** (face); **Suspected exposure site** - skin of neck. **Presentation** - facial swelling, laryngeal edema, suffocation	Autopsy report of "anthrax"	Spontaneous delivery at home 3 days before maternal death

Danesbod (1970); Iran	"term"	**Cutaneous** (face); **Suspected exposure site** - skin of neck. **Presentation** - facial swelling, laryngeal edema, suffocation	Autopsy report of "anthrax"	Spontaneous delivery at home 3 days before maternal death. Maternal death a few hours after presentation to hospital.
Vogt (1927); Germany	5 months postpartum	**Cutaneous** (hand); **Suspected exposure** - slaughtering a sick cow 5 days prior to seeking treatment. **Presentation** - fever, deep wound covered in pus with discolored scab, pain in left arm with blisters and black scab , hemorrhagic lymphangitis, swollen arm and extremely painful, headache, sleeplessness, loss of appetite, diarrhea; **Treatment** - debridement of wound, packed with acetic clay, caffeine, suprarenin, digitalis, alcohol. Wounds treated with boric ointment.	"Anthrax bacilli were clearly detected in wound" ; characteristic skin changes	Resolved in 6 weeks; Healthy infant

Figure 1.

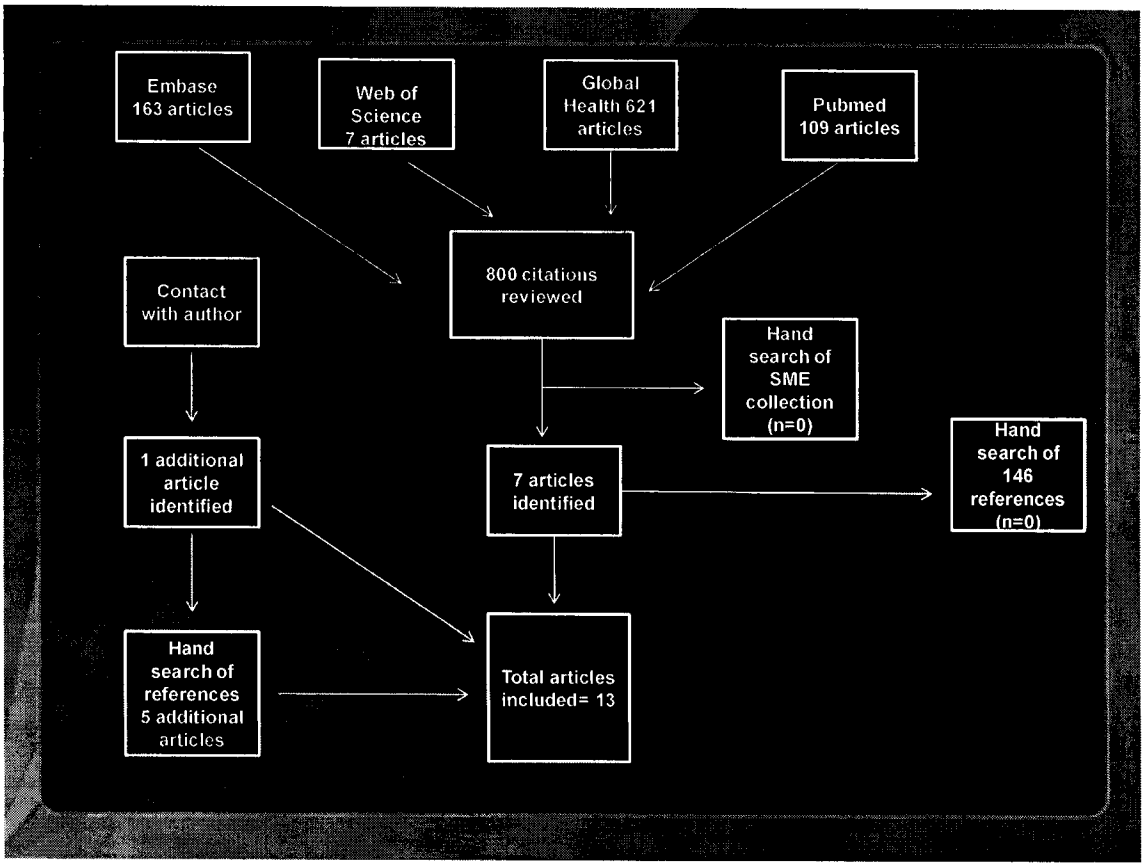

Figure 1. Legend

Abstracts and papers reviewed, and papers meeting inclusion criteria, for systematic review of anthrax in pregnant and postpartum women.

SME, subject matter expert

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Chapter IV. - Conclusion

The threat of a United States bioterrorist attack with *B. anthracis* still exists and many federal agencies, most prominently the Centers for Disease Control and Prevention, are dedicated to creating and maintaining emergency preparedness plans, to protect and guide the nation in the event of an attack (CDC website 2012). For the past 10 years, prioritization had been given to ensuring the public health recommendations are based on the most updated and available evidence, and therefore the guidance documents have been revised twice, based on emerging data. The CDC has developed 3 guidance documents pertaining to anthrax, the first immediately following the anthrax attacks in 2001 and subsequently, 2 revised recommendation documents, published in 2008 and 2010 (Stern 2008, Wright 2010). After the September 2011 Institute of Medicine's report depicting anthrax as a continued threat (IOM 2011), the CDC again embarked on the policy process to re-evaluate the 2010 anthrax guidance, through critical analysis of the data and consultation with subject matter experts in anthrax. These guidelines pertain to the general population, but specifically reference the special populations of pregnant and lactating women.

With increasing awareness of infectious risks to pregnant and postpartum women that arose from the 2009 H1N1 pandemic (Mosby 2011, Louie 2012) and the need for pre-event planning, the Division of Reproductive Health (DRH) within CDC submitted an internal proposal to formalize an emergency preparedness response focused on pregnant, postpartum women and their newborns. As a result, key members from DRH were invited to participate in the development of new emergency preparedness guidance. Beginning in May 2011, individuals form DRH began the development of emergency preparedness construct for bioterrorist agents and the Maternal Child Health Workgroup for Preparedness

Planning was formed. Subsequently, as anthrax became the top priority as a bioterrorist agent, a formal Anthrax Management Team (AMT) was formed at CDC, with representation from DRH. As members of the anthrax medical countermeasures branch of the AMT team began the process of re-evaluation and revision of the guidance, reproductive health specialists were invited to weigh in on the important issues that pose unique challenges for pregnant and postpartum women.

The original 2001 CDC guidance for anthrax preparedness did include provisions for pregnant and lactating women (MMWR 2001), and in 2011 the AMT team was charged with the critical analysis of all of the existing recommendations, including those pertaining to pregnant and postpartum women. As the policy process continued, DRH members participated in the selecting subject matter experts for participation in the anthrax policy discussions, with specific knowledge about pregnant and postpartum states. In addition, DRH members were invited to participate in the 2 anthrax meetings convened to address guidance revisions; the Expert Panel Meeting on Anthrax Clinical Management and the Anthrax Antitoxin and Post-exposure Prophylaxis Workshop. The ultimate goal at the culmination of both of these meetings was to draft new guidance for anthrax post-exposure prophylaxis and treatment for the general population as well as for special populations. However, through these meetings, it became obvious that both pediatric and obstetrical issues required additional discussion before the guidance could be formally drafted. In order to address the unique needs of the pediatric and obstetrical populations, 2 additional meetings were planned, with an August 2012 meeting dedicated to the obstetrical issues.

As the DRH group prepares for the CDC meeting focused on issues during pregnancy and the postpartum period, the limited evidence with regard to anthrax in pregnant and postpartum women became evident. It was decided that a systematic and comprehensive review of the worldwide cases of anthrax in pregnancy be undertaken, followed by a systematic review of the antibiotics and other medical countermeasures that could be used during an anthrax event. This is the first of two reviews that will accumulate the limited

evidence of anthrax during pregnancy and the postpartum period, and will serve as the foundation for discussion among a panel of obstetrical and neonatal experts at the August 2012 meeting. In efforts to better inform the discussion and decisions made about guidance discussion at this meeting, the review was conducted in a comprehensive, systematic manner and was able to identify 19 cases of anthrax infection among pregnant and postpartum women dating back to 1886.

The results of the review, as outlined in the manuscript included above and submitted to the journal, *Obstetrics and Gynecology,* reveal some unique patterns about anthrax during pregnancy and the postpartum period. The most important finding elucidated in this systematic review was the 5 cases where there was evidence of perinatal transmission by autopsy. Although these cases are over 75 years old, the demonstration of the anthrax bacilli in fetal tissues is concerning and may result in the modification of antibiotic recommendations, such that antibiotics that cross the placenta are given a higher priority for use as treatment for anthrax. In addition, this evidence combined with the high incidence of maternal and fetal deaths may improve the acceptance, by the medical community, of the recommendations for the use of nontraditional agents, such as ciprofloxacin, and doxycycline as well as the anthrax vaccine, for which there is limited safety data in pregnancy. If anthrax is deemed to have a higher risk of fatality among pregnant women or their fetuses, this may shift the risk- benefit analysis for many clinicians and thereby lead to greater use of these agents, in both the treatment and the post-exposure prophylaxis setting.

In addition, the current recommendations indicate that pregnant women should only receive the anthrax vaccine in the post-event setting, along with 60 days of antibiotics. If the threat of perinatal transmission is considered real, then it may be that the anthrax vaccine may even be recommended in the pre-event setting for certain groups of pregnant women. This approach is seen with other vaccines given during pregnancy, as protection not only for the mother, but for the fetus as well.

The review has identified three cases of cutaneous anthrax that were associated with preterm deliveries. Although this evidence will need to be carefully reviewed by expert panelists at the August meeting, it may lead to formal recommendations, pertaining not only more aggressive treatment, but perhaps increased monitoring of pregnant women who are exposed to or infected with anthrax.

Lastly, the higher than expected incidence of death from cutaneous anthrax infections may be explained by the timeframe of the disease and the lack of effective antimicrobials. However, the mortality proportion (54%) is higher than would be expected for untreated cutaneous anthrax (10-40%), and this does raise the possibility of more severe cutaneous anthrax in this at-risk population. As a result, the new guidance may suggest that cutaneous anthrax be treated with different antibiotics or with a greater number of antibiotics in pregnant women and postpartum women. At the very least, cutaneous anthrax during pregnancy may require more careful monitoring that among the general population, a decision that , in general, is easily achieved and seems prudent given that two lives are at stake.

Overall, this systematic review contributes unique knowledge to the existing medical literature by summarizing the natural history of the 19 cases of anthrax in pregnant and postpartum women. Although there may be some cases that were not identified, either because they have not been reported in the published literature or were missed through the systematic review schema devised, these 19 cases provide information on 14 more cases than were previously known. The one major gap that this review failed to provide is the identification of any confirmed inhalational cases, upon which to base the updated guidance. Although this is unfortunate, perhaps it reflects that pregnant and postpartum women are less susceptible to this form of the disease, or that the mortality is so great that the disease is not being diagnosed. Additional research, perhaps using animal models, will need to answer this question, in the absence of a bioterrorist event and if an event were to occur, the importance of a data capturing plan for

pregnant and postpartum women cannot be overemphasized.. This review not only highlights the need for more research regarding the natural history of anthrax during pregnancy and lactation, but also stresses the importance of including pregnancy status as part of the standard reporting schema for anthrax disease worldwide.