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MATERNAL-FETAL MEDICINE

The etiology of maternal mortality in developed countries: a systematic review of literature

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Abstract
Purpose To review the literature about MD in developed countries.
Methods A search in PubMed, EMBASE, Medline and reference lists was performed. Key words: maternal death/mortality, pregnancy death and obstetric/maternity care. Articles were selected if they reported the cause of death per livebirths, were performed in developed countries and unselected population, classified MD by the World Health Organization. Maternal age, cause of MD, time of MD (antepartum, intrapartum, postpartum) and delivery mode were abstracted. MD was expressed as maternal mortality ratio (MMR). PRISMA guidelines were followed.
Results Twelve articles provided data from 1980 to 2007. The MD rate was 9,750 in 75,560,683 livebirths (MMR: 12.90). MD was direct in 6,791 women (MMR: 8.98), being postpartum hemorrhage the leading cause, and indirect in 2,786 women (MMR: 3.68), with cardiovascular disease as the main cause. The remaining 173 deaths (MMR: 0.22) were unexplained. Maternal age >45 years, vaginal delivery, postpartum period increased the risk of MD. MD reduced over time in all countries except in the Netherlands and USA.
Conclusions Conditions leading to hemorrhage warrant strict management. The risk of an apparently healthy woman to die during motherhood is 0.22 out of 100,000 livebirths.

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Keywords Maternal mortality/death · Developed country · Pregnancy death · Obstetrical care

Introduction

Maternal mortality caused by pregnancy and its complications is an important topic for clinical medicine and represents a public indicator of health care systems. After the Second War, a decline of maternal mortality was observed in developed countries due to socioeconomic development, improved health care services and emergency obstetric care [7]. In spite of this, maternal mortality remains the major cause of death among women of reproductive age in many countries [18]. Because most pregnancy-related deaths are preventable, the reduction of pregnancy-related deaths continues to be a primary public health goal [10].

The identification of factors leading to maternal death differs by countries due to unequal prevalence of diseases and codification of maternal death in vital statistics. Nonetheless, analysing the causes of maternal mortality may contribute to the understanding of maternal trends over timing. In addition, the knowledge of maternal mortality etiology may assist in developing protocols for the identification of high-risk subpopulation who may benefit from careful management.

The aim of this review was to examine the literature for the causes of maternal death in developed countries and highlight limitations of the literature upon this relevant topic.

Materials and methods

A search of PubMed, EMBASE, Medline, Cochrane library and reference lists was performed for relevant publications

that described maternal mortality during pregnancy and the year following pregnancy. The search was performed in the period 2000–2011. Key words were: maternal mortality, maternal death, pregnancy-associated death, safe motherhood and obstetrical care. Articles were eligible for inclusion if they reported the cause of death per live births, were performed in developed countries, were based on unselected population, and reported data as exact rates. Exclusion criteria were: omitting at least one inclusion criterion, data reported in graphs or percentage, case reports and non-English language publications. Studies were selected according to the PRISMA guidelines and Cochrane Collaborative's tool for assessing risk of bias concerning sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias have been strictly followed.

The two authors independently selected articles and disagreement was resolved with consensus.

From each article, the incidence of maternal mortality per live births, maternal age, cause of maternal deaths, timing of maternal death (antepartum, intrapartum, postpartum, late deaths), and mode of delivery were abstracted.

An attempt to contact the corresponding author was performed in order to obtain unpublished or incomplete data.

Maternal deaths were classified as proposed by the World Health Organization as follow:

- Direct obstetric death: deaths resulting from obstetrics complications of pregnancy, from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above.
- Indirect obstetrics deaths: deaths resulting from previous existing disease, or diseases developed or aggravated in pregnancy but not due to direct obstetrics causes.
- Non-pregnancy-related maternal deaths: coincidental deaths unrelated to pregnancy.
- Late maternal deaths: deaths occurring between 42 days and 1 year after abortion, miscarriage or delivery that is due to direct or indirect obstetrics causes.

The maternal mortality ratio (MMR) was calculated as the number of deaths per 100,000 live births (number of maternal deaths, divided by the live births, multiplied by 100,000).

Results

Figure 1 shows the steps of the review. Characteristics of each study are reported in Table 1. Twelve articles were

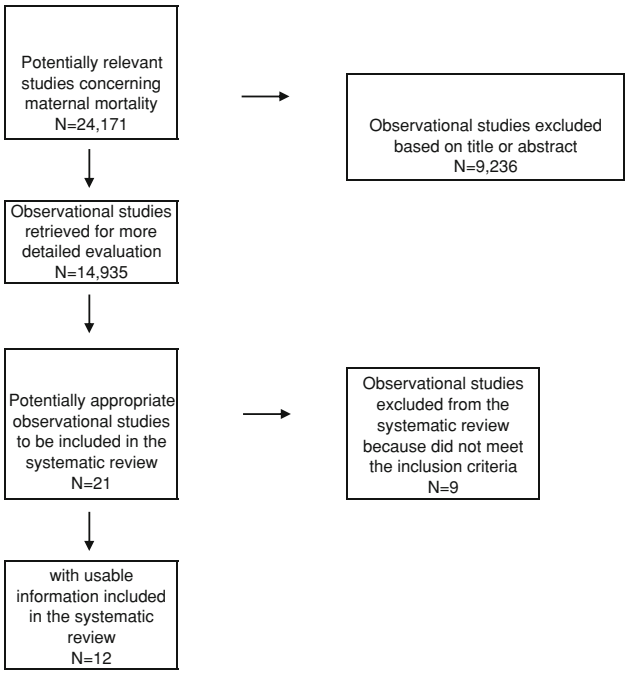

Fig. 1 Steps of the review

available [1–5, 7, 11, 13, 17, 19–21]. Articles collected data from 1980 to 2007. The overall mortality rate was 9,750 in 75,560,683 live births, which resulted in MMR equal to 12.90 per 100,000 live births. Maternal mortality was defined as direct in 6,791 women (MMR: 8.98), indirect in 2,786 women (MMR: 3.68), and unexplained in 173 women (MMR: 0.22).

The most frequent direct cause was hemorrhage (MMR: 2.03), followed by hypertensive disorders (MMR: 1.82), sepsis (MMR: 1.41), thrombosis/thromboembolism (MMR: 1.34), amniotic fluid embolism (MMR: 0.92), abortion (MMR: 0.08), ectopic pregnancy (MMR: 0.07), and anesthetic complications (MMR: 0.17). There were 766 (MMR: 1.01) deaths that could not be classified in a single group because of their heterogeneity, and 91 (MMR: 0.12) deaths due to etiologies unspecified in the articles but reported as "other causes". The indirect causes of maternal mortality were represented mainly by cardiovascular disease (MMR: 1.28), followed by complications of central nervous system (MMR: 0.66), sepsis (MMR: 0.05), pulmonary (MMR: 0.02), and gastrointestinal tract diseases (MMR: 0.01). There were 27 (MMR: 0.03) deaths that were miscellaneous (acute pancreatitis, complications associated with liver diseases, immune disease) and 1,228 (MMR: 1.62) attributed to unspecified etiology, reported as "other causes". Table 2 outlines the incidence of each cause leading to maternal death.

Non-pregnancy-related maternal death was assessed in three articles [5, 7, 17] and accounted for 111 of 5,521,842 (MMR: 2.01). Late maternal death was described in two

Table 1 Characteristics of the included articles

Author	Year of publication	Region	Study period	Live birth	Total death	MMR per year
Nagaya	2000	Japan	1991–1992	2,432,179	197	4.05
Dimitrakakis	2001	Greece	1980–1985	800.026	74	1.54
			1986–1995	1,043,599	52	0.49
Vrachis	2010	Greece	1996–2006	1,143,342	29	0.23
Berg	2003	USA	1991–1997	27,886,000	3,201	1.64
Berg	2010	USA	1998–2005	32,347,794	4,693	1.81
Welsch	2004	Bavaria	1983–1988	699.663	96	2.28
			1989–1994	793.222	63	1.32
			1995–2000	756.426	72	1.59
Gurina	2006	Russian Federation	1992–1994	108.332	103	31.7
			1995–1997	101.755	47	15.4
			1998–2000	92.69	44	15.82
			2001–2003	113.265	47	13.83
Zhu	2008	Shangai	1996–2005	819.599	243	2.96
Romero-Gutierrez	2007	Mexico	1992–2004	232.278	112	3.71
Fassler	2010	Switzerland	1995–2004	771.206	46	0.59
Schutte	2010	Netherland	1983–1992	1,860,807	184	0.98
			1993–2005	2,557,208	329	1
Donati	2011	Italy	2000–2007	1,001,292	118	0.02

MMR maternal mortality ratio

articles [5, 17] and consisted in 52 cases of 5,189,221 live births (MMR: 1.00).

Maternal mortality for age could be pooled from four articles [5, 11, 17, 20] and was reported in women aging from ≤19 to ≥45 years. There were 830 maternal deaths in 7,594,460 live births. The highest MMR was observed in women ≥45 years old (MMR: 163.73) and the lowest MMR was noted among women 20–24 years old (MMR: 7.07) (Table 3).

Four articles calculated mortality rates according to mode of delivery [5, 11, 13, 17]. Cesarean sections included both elective and emergency deliveries, and vaginal deliveries composed of both spontaneous and operative deliveries. Maternal mortality rate was reported as 143 for 7,853,678 cesarean deliveries (MMR: 1.82), and 139 out of 3,258,457 for vaginal deliveries (MMR: 4.26).

Timing of maternal mortality was reported by three articles [7, 11, 20], hence timing was accounted for in only 507 of 1,583 deaths. Of these, 193 were antepartum deaths (38.07 %; MMR: 3.85), 111 cases occurred intrapartum (2.17 %; MMR: 0.22), and 303 in the postpartum period (59.76 %; MMR: 6.05).

Four countries reported MMR trends over the last years. In Greece, Bavaria and Russian Federation there was continual decline of MMR per year, whereas in the Netherlands and United States MMR per year (MMR divided by number of years in the study period) mildly increased from 0.98 to 1.00 and from 1.64 to 1.81, respectively. In particular, the additional cases were attributed mainly to direct causes except anesthetic disorders in the Netherland, and to cardiovascular and CNS disorders in USA.

Discussion

This reviews shows that pregnancy-associated maternal mortality ratio accounts for ~13 per 100,000 live births. Of these, 79 % results from direct obstetrics causes and 24 % results from adverse conditions that develop or worsened during pregnancy. Noteworthy, 0.22 deaths per 100,000 live births are associated with unknown etiology. This finding indicates that the risk of an apparently healthy woman to die during or shortly after her pregnancy is 0.22 per 100,000 live births in the absence of risk factors.

We observed that the highest maternal mortality rate was due to hemorrhage, being placental abruption and uterine rupture the leading factors. A possible explanation could be the lack of standard definitions of severe hemorrhage and its management [14]. Studies on this topic would probably be helpful to reduce death due to hemorrhage. The second cause of maternal mortality was attributed to hypertensive disorders. In the Netherlands, preeclampsia revealed to be the major cause of maternal mortality [16] and its incidence increased in the period 1983–2005. Insufficient diagnostic testing, inadequate management of hypertension and failure to consider timingly delivery

Table 2 Causes of maternal death

Causes	Incidence, *n* (%)	MMR
Direct		
Hemhorrhage	1,539 (22.7)	2.03
Hypertensive disorders	1,375 (20.2)	1.82
Sepsis	1,069 (15.7)	1.41
Thrombosis/thromboembolism	1,015 (14.9)	1.34
Amniotic fluid embolism	694 (10.2)	0.92
Anesthetic	127 (1.9)	0.17
Abortion	59 (0.9)	0.08
Ectopic pregnancies	56 (0.8)	0.07
Other	766 (11.2)	1.01
Unspecified	91 (1.3)	1.3
Total	6,791 (69.6)[a]	8.98
Indirect		
Cardiovascular	972 (34.9)	1.28
CNS	501 (18.0)	0.66
Sepsis	36 (1.3)	0.05
Pumlonary	14 (0.5)	0.02
Gastrointestinal	10 (0.36)	0.01
Other	1,228 (44.0)	1.62
Unspecified	27 (0.9)	0.03
Total	2,786 (28,6)[a]	3.68
Unexplained	173 (1,8)[a]	0.22
Total	9,750	12.90

n number, *MMR* maternal mortality ratio

[a] Percentage out of the total deaths

Table 3 Maternal mortality for age

Age	Incidence, *n* (%)	Live births	MMR
<19	21 (2.53)	131,715	15.94
20–24	81 (9.76)	1,146,129	7.07
25–29	232 (27.95)	2,903,131	8
30–34	270 (32.53)	2,442,290	11.05
35–39	164 (19.75)	842,917	19.45
40–44	54 (6.50)	123,392	43.76
>45	8 (0.96)	4,886	163.73

appear to be responsible for the fatal outcome. A strict follow-up of women with hypertensive disorders would prevent its fatal outcome. Great discrepancy was noted between the studies, as most reported thromboembolic causes of death as the most infrequent while in two other articles [2, 20] this was the most frequent cause. Authors failed to report the prevalence of coagulation defects in the studied population as well as the rate of preventive anticoagulation medical therapy. With regard to indirect causes, theoretically all the organ systems may be injured during pregnancy so severely to result in maternal death. We found that cardiovascular disease was the most frequent cause of maternal mortality, followed by complications of central nervous system, infections, pulmonary, and gastrointestinal tract diseases. The trend of maternal mortality by timing shows an increased incidence of maternal death for indirect causes. Indirect causes indicate the presence of unrecognized risk factors that manifest during or because of pregnancy and give rise to severe complications. It may be speculated that a careful search of these factors by investigating women's health history antenatally or by preconception care might be helpful in reducing maternal death for indirect causes.

Current literature is characterized by paucity of information with regard to late deaths and non-pregnancy-related deaths, which are described in only two and three articles. A possible explanation might be that late deaths and non-pregnancy-related deaths are unlikely to be under the care of an obstetrician and 9 out of the 12 reviewed articles were published in obstetrical journals. Therefore, late deaths and non-pregnancy-related deaths might be underreported.

According to our findings, the advanced maternal age is associated with a higher risk of maternal death compared with younger ages, probably because the prevalence of chronic disease, such as hypertension and diabetes, increases with age. This result is very important in the light of the constant increase of advanced maternal age at first pregnancy.

When the mode of delivery was studied, maternal mortality rate was slightly higher among women who delivered vaginally than by cesarean section. Noteworthy, articles did not distinguish between operative or spontaneous delivery and elective or emergency cesarean sections and did not report whether maternal death was secondary to complications of delivery mode or underlying conditions.

Further studies on this topic are warranted in order to define if type of delivery represents a significant risk factor for maternal mortality.

Limitations of our review, that are due to lack of information from the literature, should be acknowledged. Indirect causes may depend on a suboptimal general health status of women in the reproductive period. Romero-Gutierrez et al. [13] showed by a regression model that maternal age, marital status, number of antenatal visits, previous obstetrics complications and preexisting medical conditions are significantly associated with maternal mortality. Therefore, a detailed investigation of risk factors before conception may be useful to identify, since the early stages of pregnancy, women at elevated risk of death. Nonetheless, the reviewed articles are characterized by paucity of data about maternal preconceptional history and risk of subsequent death.

Maternal mortality rates differ between residents and migrating population due to major socioeconomic status, cultural factors and lack of access to maternity care [8, 12, 21]. However, there were few data to distinguish between residents and non residents in the articles pooled in this review.

It is reasonable to assume that maternal mortality rate has reduced over timing due to improvement of obstetrical care and hospitalization in the last decade. For instance, in Greece a progressive reduction of maternal mortality per year was observed from 1983 (MMR: 2.28) [3] to 2006 (MMR: 0.23) [19]. Similar reductions were observed in Bavaria [20] and Russian Federation [7]. Although we selected articles published in the period from 2000 to 2011, some articles included cases of maternal death before 1999. These differences in the study periods might have biased our results.

Finally, most of the studies are based on death certificates that might have been coded by non-medical personnel without identification and correction of data leading to entry mistakes and coding errors. The rates of underreported rates of maternal death ranged from 20 % in Switzerland [5] and 26 % in the Netherlands [15] to 38 % in Austria [9] and 60 % in Finland [6]. A possible explanation to this might be overlooked checkboxes of pregnancy status on death certificates.

In conclusion, hemorrhage, an obstetric complication, is the main cause of maternal mortality. In approximately 0.22 per 100,000 pregnancies maternal mortality is unexplained and life-threatening conditions are unpredictable. Improvements of registration and supplemental information are necessary to make recommendations for future obstetric care.

Conflict of interest None.

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