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Maternal mortality and thromboembolic risk in pregnancy

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A B S T R A C T

Every year, around the world over half a million women die for pregnancy related complications. In developing countries one woman in 16 dies compared to one in 2,800 in developed countries.

Prevention programs based on the right knowledge can avoid many of these deaths, even in resource poor countries.

In this review will be taken into account maternal deaths in developed countries (less than 1% of the global maternal death rate).

In order to reduce maternal mortality, one must answer the following five questions:

1. How many mothers die?
2. Which kind of mother die?
3. Why mothers die?
4. Was maternal death avoidable?
5. What can be done to prevent them?

However, maternal deaths are difficult to quantify, even in countries where the civil registration of deaths and of their causes is careful. In fact, countries with an accurate recording system like Italy underreport maternal mortality rates.

Measuring the maternal mortality rate is only the first step to approach the problem and different ways have been developed to quantify it.

But only the *Confidential enquiries into maternal deaths* registry has demonstrated that it could answer the above five questions regarding maternal death. It must become a Government requirement that all maternal deaths should be subject to this Confidential enquiry and all health professionals should provide these data.

The authors, together with professor Patrizia Berto from Verona University, have carried out a cost benefit analysis of adopting a *Confidential enquiry into maternal deaths* registry in Lombardy, a region of Northern Italy. We have demonstrated that applying our program we could save at least two women's lives each year in Lombardy, with a cost per year of life saved of € 60,000/100 LYG = 600 €/LYG.

As in other developed countries, in Lombardy, like in Italy itself, venous thromboembolism is a major cause of maternal mortality. The physiological changes of

pregnancy and other factors, such as maternal age, parity, obesity, operative delivery, general anaesthesia and congenital and acquired thrombophilia, further increase the risk of VTE throughout pregnancy and puerperium.

The *Confidential enquiries* have invariably demonstrated that thromboembolic induced maternal deaths surely belong to the category of avoidable maternal deaths.

From year 2000, in our General Hospital Obstetric Department we applied the principle of Risk Management to define thromboprophylaxis guidelines following caesarean delivery. From January 2000 to September 2005 we have seen five cases of postcesarean delivery pulmonary embolism. In these years, the number of all caesarean deliveries was 2,307. This means that we have seen one case of pulmonary embolism (objectively documented with pulmonary scintigraphy) each 461 caesarean deliveries. In two cases thromboprophylaxis had not been performed whereas in the other three cases prophylaxis had been performed at a reduced dosage. We did not record a case of thromboembolic maternal death.

Although in our Department the implementation and routine application of thromboprophylaxis guidelines has dramatically reduced the number of postcesarean delivery thromboembolic episodes, there has been a rise in thromboembolic episodes rates in women with vaginal delivery, in many of whom the diagnosis was missed. This is a concern mostly in women who, in spite of known risk factors, was not offered the appropriate thromboprophylaxis. For this reason in year 2005 we decided to extend thromboprophylaxis guidelines to vaginal

deliveries. In order to modify our practice based on these observations we implemented an audit program to regularly discuss the guidelines operating in our Obstetric Department with the goal to further improve compliance with international and hospital guidelines. Knowing total maternal mortality rates is not enough: we must understand factors underlying each case of death. Each maternal death or life threatening complication has a story to tell us and can provide indications on the practical ways of addressing the problem.

Maternal mortality

In ancient times, giving birth was an extremely dangerous and risky event.¹⁻² As tombstones tell us, it was not uncommon for the women to die giving birth. In recent years, reduction of maternal mortality rate has been endorsed as a key development goal by many countries and this objective is included in the consensus documents produced by the following international conferences:

- the World Summit for Children (1990)
- the International Conference on Population and Development (1994)
- the Fourth World Conference on Women (1995) and the related five year follow-up evaluations of progress (1999 and 2000)
- the millennium Declaration (2000)
- the United Nations General Assembly Special Session on Children (2002).

However, today every year over half a million women

still die giving birth around the world. In developing countries, one woman in 16 may die of pregnancy related complications compared to one in 2,800 in developed countries.³ This means that every minute somewhere in the world a woman dies for causes related to pregnancy or childbirth. These causes are listed in Figure 1.

But many of these deaths could be avoided. Avoiding maternal deaths is possible even in resource poor countries if the implementation of preventive programmes is based on the right kind of knowledge. In developing countries the key problem is that only about half of the deliveries is assisted by a skilled birth attendant (a doctor, a midwife, a nurse or a community worker with midwifery training).

In Sri Lanka for instance, implementing the so called Mother Baby Package and improving female education the government reduced remarkably the maternal mortality ratio, currently one of the lowest in the developing world (60 per 100 000 live births).⁴⁻⁵

In this review we will address the topic of the maternal deaths in the developed countries: less than 1% of global maternal deaths happens in developed countries. Although small, this rate is not negligible. For instance, in the UK the Maternal Mortality Rate in 2000-2002 was 13.1 deaths per 100,000 maternities.⁶ In developed countries the causes of maternal death are different from those recorded in resource poor countries and from the global distribution of maternal mortality causes all over the world. Figure 2 lists the causes of maternal death in the UK.

Some definitions can help us to quantify the issue of

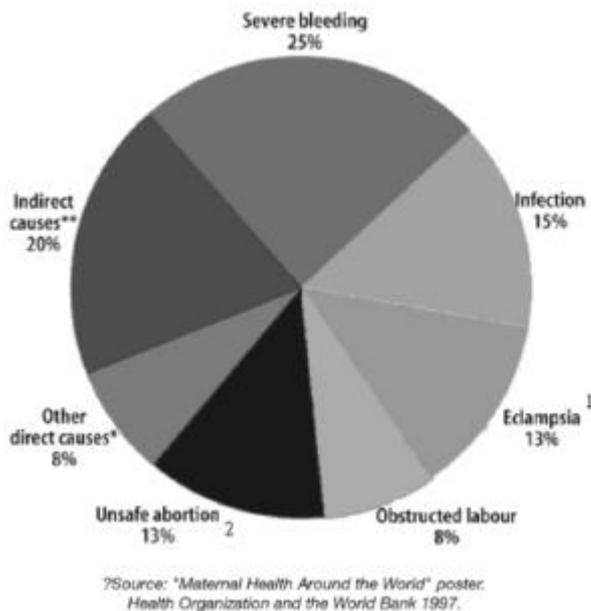


Figure 1. Causes of maternal death in the world.

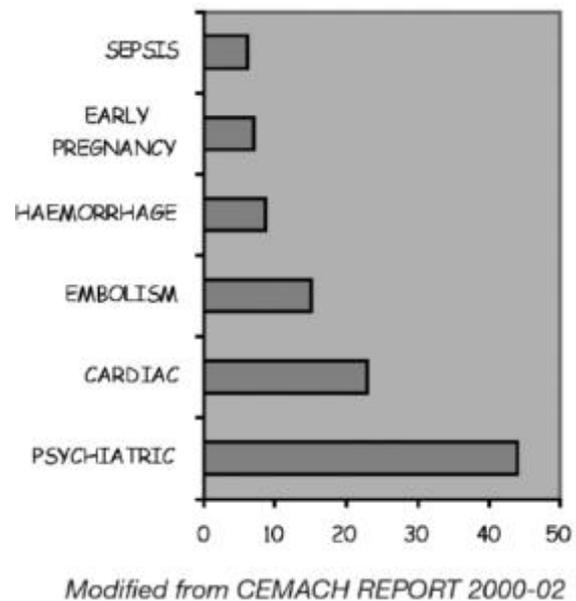


Figure 2. Causes of maternal deaths, rate per million.

Table 1. Underreporting rates of maternal mortality rates.

<i>Nation</i>	<i>Underreporting rates</i>	<i>Reference</i>
France	56%	9
The Netherlands	26%	10
Austria	38%	11
Finland	60%	12
Italy/Lombardy	50%	13-14

maternal deaths.

A maternal death is defined as: *the death of a woman while pregnant or within 42 days of termination of pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes* by the 9th and 10th revision of the International Classification of Diseases, Injuries and Causes of Death (ICD9/10).⁷⁻⁸

Maternal deaths can be classified:

- as direct maternal deaths, i.e. those resulting from conditions or complications (or their management) that are unique to pregnancy, occurring during the antenatal, intrapartum or postpartum period;
- as indirect maternal deaths, i.e. those resulting from previously existing disease or disease that develops during pregnancy and which were not due to direct obstetric causes but which were aggravated by the physiologic effects of pregnancy.

In order to try to reduce maternal mortality rate, we must answer the following questions:

1. How many mothers die?
2. Which kind of mother die?
3. Why mothers die?
4. Was maternal death avoidable?
5. What can be done to prevent them?

To reduce the rate of maternal deaths, first of all it is important to know the magnitude of this problem. The maternal mortality ratio is one of the best indicators of the *quality of life* of women living in a country, i.e., of their access to healthcare, and of the adequacy of the health care system in responding to their needs. However, it is difficult to quantify this rate, also when civil registration of the numbers and of the causes of deaths is careful. There are three main causes of error in reporting maternal death rate:

- frequency of maternal mortality is low;
- maternal deaths are frequently underreported;
- maternal deaths are often misclassified.

We can classify all countries in the following four categories concerning the reporting of death rates:

1. countries with an accurate civil recording and correct identification of causes of death. But even there, misclassification of maternal deaths can arise, for example, if the pregnancy status of the woman was not known nor recorded, or the cause of death was

wrongly ascribed to a non-maternal cause;

2. countries with a relatively accurate civil recording of births and deaths but where causes of death are not adequately classified. In fact, causes of deaths are routinely reported only in almost 78 countries or areas around the world, covering approximately 35% of the world's population;

3. countries with no reliable system of civil recording where maternal deaths (like other life events) go unrecorded. Currently, this is the case for most countries with high maternal mortality rates;

4. countries where estimates of maternal mortality are based on household surveys, usually using the direct or indirect sisterhood methods. However countries with a good recording system (as Italy) also underreport maternal mortality rates (Table 1).

Two surveys conducted independently from Lombardy's Society of Obstetrics and Gynaecology (AOGOI) reported a rate of maternal mortality of 13/100,000 maternities in the years 1996-1998 and of 7/100,000 in the year 2004.¹³⁻¹⁴ Although lower than those reported for instance for France (18/100,000) (9) these data are 2-3 times higher than those reported by the Italian National Institute of Statistics (ISTAT).¹⁵

Measuring the maternal mortality rate is the first step to approach the problem and different ways have been developed to quantify it. The more important methods are:

- *Vital registration*. In developed countries, maternal mortality is measured using data on births and deaths collected through vital registration systems combined with medical certification of the causes of death. But this system is not perfect at all, and maternal deaths are often misclassified resulting in underreporting of maternal mortality rates.

- *RAMOS* (Reproductive Age Mortality Surveys). These studies involve in depth reviews of deaths among all women of reproductive age. They are considered the *gold standard* for estimating maternal mortality. Unfortunately they are complex and costly.

- *Household surveys*. This is a direct method that requires a very large sample to provide reliable and representative results because maternal deaths are luckily rare events. The confidence intervals are typically wide, and thus maternal mortality indicators are imprecise.

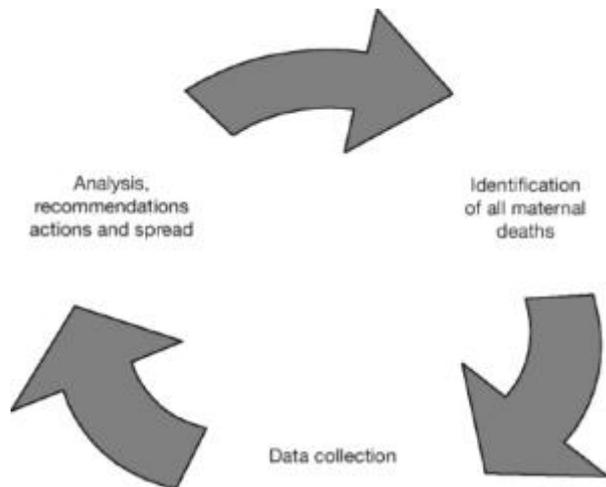


Figure 3. Principles of a Confidential enquiry into maternal deaths survey.

- *Sisterhood Method*. This is an indirect method consisting in surveying women of reproductive age and asking them a series of questions about the survival of all their adult sisters. But the sisterhood method does not provide an estimate of current maternal mortality rates and therefore does not reflect any change that may have occurred over last few years.
- *WHO/UNICEF Estimates*. This method, developed in the year 1990 by WHO and UNICEF, involves a dual strategy: 1) where maternal mortality estimates already existed, the figures were adjusted to account for underreporting and misclassification; 2) where no reliable estimates were available, a model was applied that generates an estimated figure based on fertility rates and the proportion of births assisted by a skilled birth attendant. Data obtained by this method are not very accurate and are to be considered as providing only a rough estimate of these phenomena.
- *Verbal autopsy*. It is a qualitative, in depth investigation of the causes and circumstances of a small number of maternal deaths occurring at selected healthcare facilities. It requires the co operation from the family of the dead woman and sensitivity is needed in discussing the circumstances of her death.
- *Census*. It is a survey of all people and households in the country. It provides an essential data base both at national and local levels for government, business, and the community.
- *Surveys of severe morbidity, near misses*. It is the identification and assessment of cases of pregnant women surviving obstetric complications. There is not a universally applicable definition for such cases and it is important that the definition used in any survey be appropriate to local circumstances to enable local

improvements in maternal care.

- *Confidential enquiries into maternal deaths*. This is a systematic multi disciplinary anonymous investigation of all maternal deaths occurring in an area or at regional (state) or national level. It identifies the numbers and causes of death and also any avoidable or remediable factor associated with them.

The *Confidential enquiries into maternal deaths* survey can answer all the above mentioned questions (How many mothers die? Which kind of mother die? Why mothers die? Were these maternal deaths avoidable? What can be done to prevent them?).

In order to develop, implement and evaluate policy and programme efforts, understanding why women die from pregnancy and childbearing related conditions is more important than establishing the rate of maternal mortality. From this point of view, we think that in developed countries like Italy the best method is to establish a registry of Confidential enquiries into maternal death.

In other words, it must become a Government requirement that all maternal deaths should be subjected to this Confidential enquiry and all health professionals must provide the data required. The main endpoint of a confidential enquiry is to save lives by determining any inadequacy in each woman's healthcare or in the healthcare system or the community that may have contributed to her death, collating the knowledges and evidences acquired from assessing the totality of cases and recommending appropriate changes as shown in Figure 3.

This registry should be maintained both at a nationally and regional level and supported by healthcare planners, professionals and the Ministry of Health. The data provided should be enough reliable to enable the adoption purposeful measures.

The authors, together with professor Patrizia Berto from Verona University, have carried out a cost benefit analysis of adopting the "Confidential enquiry into maternal deaths" registry in Lombardy, a region in Northern Italy.

Every year in Lombardy four maternal deaths are officially recorded. As an example of the *denominator*, in the year 2001 in Lombardy has been recorded 87,737 births. We estimate that adopting the system of the Confidential enquiry we would have approximately 11~13 maternal deaths. Four of these are due to thromboembolism or sepsis,¹³⁻¹⁴ applying current guidelines for thromboembolism and sepsis prevention,⁶⁻¹⁶ we estimate that we could save at least two of these women each year. In order to develop the program, the global cost is approximately 60,000 €/year, with a cost per year of life 60,000 €/100 LYG = 600 €/LYG. (The detailed analysis of the program is available on request).

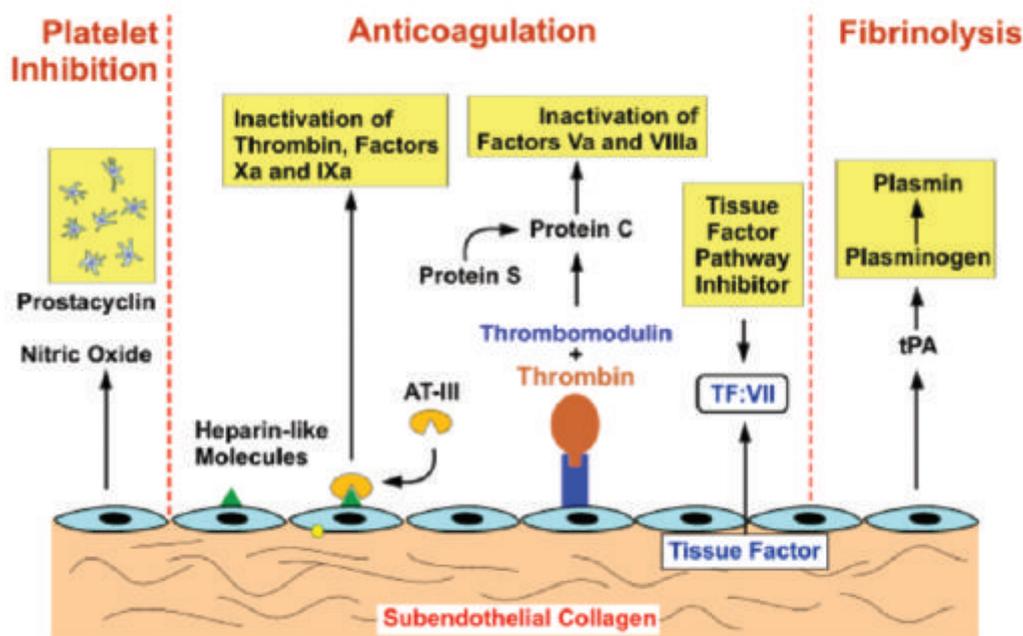


Figure 4. Coagulation balance.

Thromboembolism in pregnancy and puerperium

Normal haemostasis is a balance between factors that promote clot formation after injuries and factors that prevent inappropriate clot formation (Figure 4).

During pregnancy, the levels of several essential coagulation factors increase. In fact, there are marked increases in fibrinogen and factor VIII. Factors VII, IX, X, and XII also increase, though to a lesser extent.

Fibrinolytic activity is depressed during pregnancy and labour through a mechanism still not completely known. The placenta may be partially responsible for this alteration in fibrinolytic status. Plasminogen levels increase together with fibrinogens levels, causing a balance of clotting and lysing activity. Clearly, coagulation and fibrinolytic systems undergo major alterations during pregnancy. The physiological changes of pregnancy and other factors, such as maternal age, parity, obesity, operative delivery, general anaesthesia and congenital or acquired thrombophilia, further increase the risk of VTE throughout all three trimesters of pregnancy, and puerperium. Venous thromboembolism is a leading cause of maternal mortality in developed countries like Italy. More specifically, today thrombosis and thromboembolism are the leading direct causes of maternal death. Their incidence is 1.0/1,000 pregnancies in women ≤ 35 years of age but

it increases in women >35 years age (2.4/1,000 pregnancies): this means that thromboembolism is 5–6 times more frequent in pregnant women compared to non pregnant women of the same age.¹⁷ There are twice as many episodes before delivery than in the 6-week postnatal period. Thromboembolism is still the leading cause of maternal deaths in the UK,¹⁸ although its rate fell from 21.8 per million maternities in the 1994–1996 Report to 16.5 per million maternities in the 1997–99 Report. These deaths account for 33% of all direct maternal deaths.

However, the overall death rate hides two key findings:

- the number of deaths from thromboembolism following caesarean delivery fell dramatically following the introduction and routine use of guidelines for thromboprophylaxis (1995);
- conversely, it was reported a significant rise in the number of deaths from thromboembolism in women with vaginal delivery, in many of whom the diagnosis was missed either in general practice or obstetric departments, or in women who, despite having known risk factors, were not offered appropriate thromboprophylaxis.

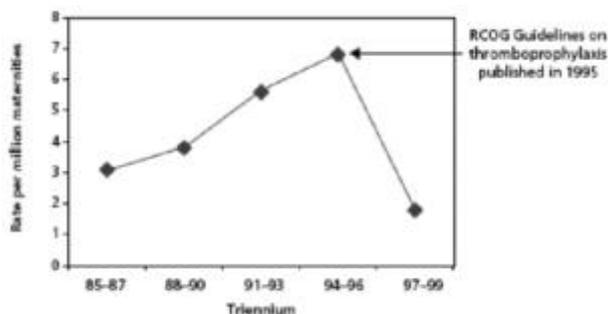
This has prompted the Royal College of Obstetricians and Gynaecologists to develop a guideline on thromboprophylaxis in vaginal delivery too.¹⁶ The enquiries have constantly demonstrated that many deaths could be avoided, and mainly thromboembolism-induced maternal deaths. To reduce the incidence of VTE a bet-

Table 2. Risk factors for venous thromboembolism in pregnancy and puerperium.

<i>Previous</i>	<i>Transient</i>
Previous VTE	Hyperemesis
Polycythaemia vera	Dehydration
Congenital thrombophilia	Ovarian hyperstimulation syndrome
	Severe infection, e.g. pyelonephritis
Antithrombin deficiency	Immobility (> 4 days bed rest)
Protein C deficiency	Hypertension / Pre-eclampsia
Protein S deficiency	Excessive blood loss
Factor V Leiden	Long-haul travel
Prothrombin gene variant	Prolonged labour c(more than 12 hours)
Acquired thrombophilia	Midcavity instrumental delivery c
Antiphospholipid syndrome	Immobility after delivery
Lupus anticoagulant	Surgical procedure in pregnancy or the puerperium, e.g. evacuation of retained products of conception, postpartum sterilisation
Anticardiolipin antibodies	Smoking
Obesity (BMI > 30 kg/m ²) either pre-pregnancy or in early pregnancy	
Age over 35 years	
Parity > 4	
Gross varicose veins	
Paraplegia	
Sickle cell disease	
Inflammatory disorders e.g. inflammatory bowel disease	
Some medical disorders, e.g. nephrotic syndrome, some cardiac diseases	

ter understanding of the risk factors involved and a better identification of women at risk of thrombosis, coupled with an effective thromboprophylaxis treatment, are required^{16 19 20 21 22 23 24 25 26 27} (Table 2).

We know that early diagnosis and treatment of VTE significantly reduce mortality rates. Since the introduction in 1995 of the RCOG guidelines on thromboprophylaxis for women undergoing caesarean delivery, there has been a great reduction in the number of women who die from pulmonary embolism in the UK (Figure 5). Based on this British experience, starting from the year 2000 in our General Hospital Obstetric Department we organized an obstetric anaesthesio-



From: *Why Mothers Die 1997-1999. The Confidential Enquiries into Maternal Deaths in the United Kingdom* page 51 fig. 2.1. Website: www.cemd.org.UK

Figure 5. Deaths from thromboembolism following caesarean delivery, rates per million maternities (United Kingdom 1985-99).

logical workgroup that introduced specific guidelines to prevent VTE in obstetric patients undergoing caesarean delivery. In short, the group applied the principles of Risk Management to thromboprophylaxis during caesarean delivery.

- Risk: *a measure of the likelihood and consequence of an occurrence.*
- Risk management: *the systematic application of management policies, procedures and practices to the tasks of identifying, analyzing, evaluating, treating and monitoring risk.*²⁸ (Figure 6).

The theory underlying the protocol and its application is based on research in a non-health care settings. In the aviation, oil, and nuclear industries, for instance, the formal investigation of incidents is well established.²⁹ The application of these principles to medicine works well, above all when predictable events are involved, like it is often the case for thrombosis events. Starting from 2000 we periodically discussed the recommendations currently operating in our Obstetric Department and modified our practice based on the observations of this audit with the goal of further improving compliance both with international and hospital guidelines. But a deep venous thrombosis is sometimes difficult to diagnose and the first sign may be an associated pulmonary embolus.

From January 2000 to September 2005, 2,302 caesarean deliveries were performed in our Department. In patients who underwent a caesarean delivery thromboembolic complication rate is higher. In our

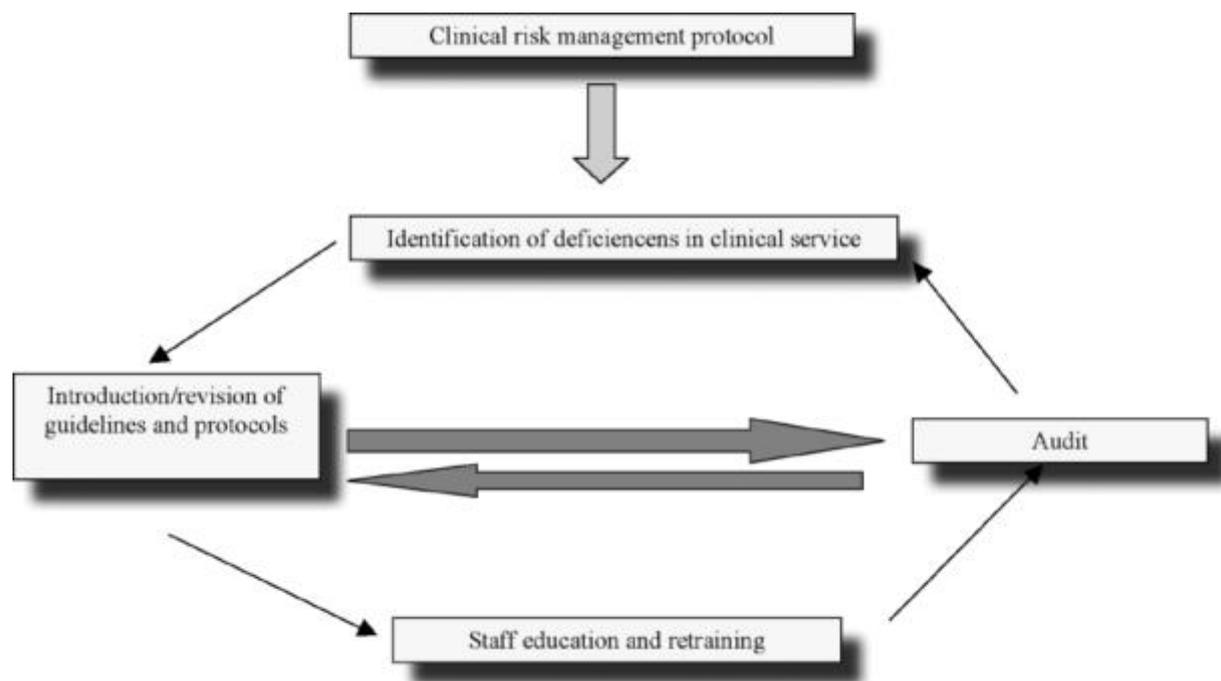


Figure 6. Clinical risk management, audit and protocols.

experience, the risk of developing a thromboembolic complication following caesarean delivery was approximately 1/1,600. If a deep venous thrombosis is not treated, up to one quarter of patients will develop pulmonary emboli, 15% of which could be fatal. In fact, we have recorded 5 cases of pulmonary embolism, but no fatal case. This means a case of pulmonary embolism every 461 caesarean deliveries. Our VTE rate is the same as that reported by medical literature.³⁰ But further improvements could be achieved. In the last Report from the UK (2000-02), VTE rate has fallen to 15.0 per million of maternity, 57% of which were assessed as receiving so called *substandard care*.¹⁸ This is also our experience: three of the five cases of pulmonary embolism (objectively documented with pulmonary scintigraphy) in our Obstetric Department

were assessed as having received *substandard care*. In fact the identification of a clear departure from good practice is usually only the first step of an investigation, but is not enough. Maternal mortality is one of the strongest indicators of differences in healthcare, both between the countries and within countries themselves.³¹⁻³² Women of different ethnic groups living in a country have a mean probability of twice or more to die than native women (Table 3). In the last few years, in Lombardy a great increase in the number of foreign patients admitted to public hospitals for pregnancy was recorded (Figure 7) and, as we know, maternal mortality may be only the tip of the iceberg of maternal morbidity and women's suffering. Good reproductive health and women's autonomy will be achieved only through community and political efforts.

Table 3. Maternal deaths and ethnic group: the UK 2000-02.

<i>Ethnic group</i>	<i>No.</i>	<i>/100,000</i>	<i>R.R.</i>
Black African	30	72.1	6.7
Black Caribbean	13	25.8	2.4
Indian	7	15.5	1.4
Pakistan	10	12.3	1.2
Bangladesh	8	22.5	2.1
Asian and others	4	5.7	0.5
Total non-white	72	31.0	2.9
White	151	10.7	1.0

Modified from: *Why Mothers Die 2000-2002 - Report on confidential enquiries into maternal deaths in the United Kingdom*. Website: <http://www.cemach.org.UK>

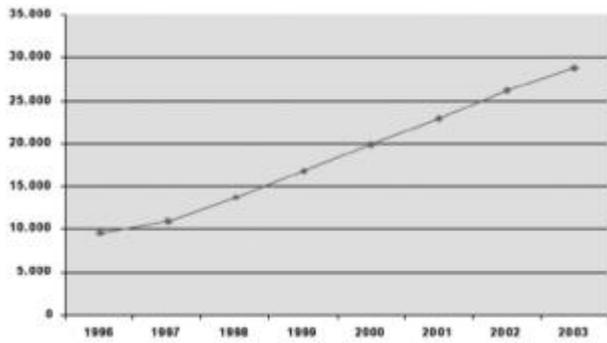


Figure 7. Obstetric hospital admissions of foreign women in Lombardy (1996-2003).

But to gain political support requires a strong-based evidence, especially when financing reproductive health services should be a global priority, that is a benefit to the society as a whole, worthy of investments in a time of strong competition for human and financial resources. For some, maternal death during

delivery is the *creative action for excellence*, the *huge expressive action represented by the creation at its apex: the creation of a new life*. This concept was explained by great Italian writer Pier Paolo Pasolini in his writing *Petrolio: In the same time when I planned and wrote my novel, that is I tried to find the meaning of reality and get hold of it, in the same creation action implied by all this, I also wanted to get free of myself, to die. I wanted to die in my work; to die as women die in giving birth...*³³

But, unlike Pasolini, we think that motherhood is the cherished dream of every woman. Why should she die? Recording the rate of maternal mortality is not enough; we must understand the underlying factors of these deaths. Each maternal death or case of life threatening complication has a history to tell and can provide useful indications on the practical ways of addressing the problem. The primary endpoint is to reduce the number of maternal deaths. A key prerequisite for reach this goal is to develop a method of reviewing maternal mortality cases.

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