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Ana Filipa Rodrigues Félix

Main Causes of Sudden Deaths in Pregnancy

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Main Causes of Sudden Deaths in Pregnancy

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TÍTULO ~~DISSERTAÇÃO~~/MONOGRAFIA (riscar o que não interessa)

Main Causes of Sudden Deaths in Pregnancy

ORIENTADOR

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ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☒

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“À minha mãe. “

Main Causes of Sudden Deaths in Pregnancy

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Abstract

Background The pregnancies represent a big physiologic change, although in the majority of the cases this alteration are easily exceed, sometimes, associated or not with previous pathologies can cause important complication to the pregnant women. The low numbers of registered cases hinder then a more specific study on the subject. The aim of this review is explore the main causes of sudden death directly and indirectly related with pregnancy.
Materials and methods Using article databases such as PubMed and books of obstetrics and legal medicine and organizations of the last ten years, we collected, and integrated information about the etiology of maternal sudden death including definition, physiopathology, epidemiology and risk factors, clinic, diagnosis, and autopsy findings.
Results The last results from Directorate-General of Health in 2013 features a maternal mortality of 8 deaths per 100000 live births. Between 2001 and 2007, in Portugal, 21.7% of the total number of maternal deaths were of unknown cause.
The main direct causes are hemorrhage/coagulation disorder, hypertensive disease of pregnancy, infection/sepsis and embolism. Pathologies such as heart and neurologic diseases, cancer disease and infection are the most important indirect causes.
Discussion Sudden death in pregnancy has a big impact in the society but actually in Europe it has been little explored.
Conclusion In order to decrease maternal death is essential the establishment of national and international reports with updated statistics and awareness of physicians to the importance of the implementation of the screening measures and treatment filed for each stage of pregnancy.

Key words: *pregnancy, sudden death, direct causes, indirect causes, autopsy*

Introduction

The World Health Organization (WHO) defines Maternal Mortality as the deaths of women during pregnancy, childbirth or in the 42 days of puerperium, independent of the duration and the local of the pregnancy. The concept of Maternal Mortality includes all the causes that can be associated or aggregated with pregnancy or its management. According to this definition, ectopic pregnancy and abortion are included in the causes, but the incidental deaths are excluded. [3] It is one of the most important indexes of the health care service of a country. [4]
The last data publish by WHO, in 2015, indicated that Maternal Mortalities are 12 and 239 per 100000 live births in developed and developing countries respectively. The first one has a lifetime risk of maternal death of 1/4900 comparing with the 1/150 in developing countries.(table 4) [2]
The absolute numbers have been decreasing in 44% in the last 25 years, with the technological evolution, better access to health care and the reduction of pregnancies in extreme ages. [2]
United Nations created the Millennium Development Goals (MDGs), which include maternal death surveillance and response (MDSR) in order to improve the precision of the notification of the deaths. The aim of MDSR was to decrease maternal mortality in 75% at 2015. The new aim is to get less than 30 deaths per 100000 pregnancies until 2030. [1] Primary prevention is, since 2015, a human right and a social concern. [1]
The current methods used to assess the maternal mortality ratio are very inaccurate and the numbers provided are not enough to recognize the major failures in diagnosis and treatment. In order to decrease the number of these errors the public health surveillance needs a

continuous interpretation of actualized data. Reliable data on maternal mortality implies an active vigilance, which requires the study of each new case. This would ideally involve an autopsy (clinical or forensic) as the circumstances demand. [3]

According to the DGS (Directorate-General of Health), in 2013, which are the last numbers in Portugal, maternal mortality is 8 deaths per 100000 live births. [5] This data is based fundamentally in clinic elements and in almost every case, the autopsy (clinical and forensic) is not included. [5]
The autopsy results are very important, because there are great discrepancies between the publish data and the real causes of death, that only can be confirm with the autopsy. This discrepancies became clear in 2008 in United Kingdom when it was performed a study with exhaustive evaluation, which included a series of autopsies. Unexpectedly, they realized, comparing with other countries, that indirect causes are more prevalent than direct causes. [6]
In 2009, a study in India proved that the discrepancy between clinical and autopsy diagnosis is more than 15%. [3] We believe that it is important to give more attention to the forensic study of maternal deaths in Portugal, in order to improve the published data and, therefore, defining health policies and be able to decrease the number of deaths.
The forensic assessment should include the clinical records, macroscopic and microscopic findings and toxicology, biochemistry and microbiological analyses. In order to do a complete autopsy study, it is important to keep in mind the specific and related pathologies, and some pathologies that can get worse with pregnancy. [3]
In maternal mortality it's known that there are four distinct categories, direct and indirect causes, coincidental and late deaths. [5]
This paper reviews the most recent published articles and the last statistical studies published by DGS and WHO, based on maternal mortality and the main direct and indirect death causes that can be neglected by doctors, leading to sudden death.
The aim is to create a review of the main pathologies that can affect pregnancy and to become a good tool for health care service, since almost every cause is preventable.
Therefore, we approach the definition, physiopathology, epidemiology and risk factors, clinic, diagnosis, and autopsy findings of each one. This work also aims to understand the role of the autopsy in sudden death during pregnancy and its possible contribution to the improvement of health care.

Materials and methods

Using article databases such as PubMed and books of obstetrics and legal medicine and organizations of the last ten years, we collected and integrated information about the etiology of maternal sudden death including the definition, physiopathology, epidemiology and risk factors, clinic, diagnosis, and autopsy findings Maternal mortality can be divided into to four categories, direct causes, indirect causes, coincidental and late deaths.

1) Maternal deaths directly related to pregnancy

Maternal deaths directly related to pregnancy include all deaths caused by obstetric problems.[7] The most frequent direct causes of maternal mortality are thrombosis and thromboembolism, pre-eclampsia and eclampsia, hemorrhagic disorders, amniotic fluid embolism and sepsis. [7]

1.1) Thrombosis and thromboembolism

Thromboembolism (VTE) is the combination of two pathologies: deep venous thrombosis (DVT), which is a condition caused by the formation of clots in the deep veins, usually in the

lower limbs (deep veins of the legs or in the pelvic veins, like the uterine veins); and pulmonary embolism, which is defined by the obstruction of lung arteries caused by clots. [8]
In the antepartum period, the pathopysiology of VTE can be explained by: (a) the venous stasis caused by the progesterone-induced venodilatation, pelvic venous compression by gravid uterus and pulsatil compression of the left and right iliac veins, (b) hypercoagulability associated with increased thrombin production, and (c) fibrinolysis reduction due to the increased plasminogen activator inhibitor type 1 and 2 activity and decreased tissue plasminogen activator activity.[8] [9]
In postpartum period, the vascular damage to the pelvic vessels that can occur after normal vaginal, assisted vaginal or cesarean section deliveries, and postpartum move restriction are the main alteration in the pathophysiology of VTE during the postpartum period. The hypercoagulability starts to decrease in the postpartum period and the risk gradually return to basal.[9]

Embolism is one of the main causes of death in pregnant woman with an estimated risk of 0,8-4,7 per 100000 maternities.[9] The highest risk of thrombosis starts with pregnancy and lasts until about two months after delivery.[8] The main risk factors to VTE are: obese pregnancy, above 35 years old, sedentary life and caesarean delivery (rather than vaginal delivery) and coagulation mutations like the factor V Leiden.[7] [8] [10]

The presence of symptoms like breathlessness, syncope, pleuritic pain, cough and hemoptysis, accompanied by the presence of signs like tachypnea, tachycardia and cyanosis should arise attention of the medicine assistant to the possibility of VTE.[10]
The diagnosis of VTE is difficult to execute and normally only 10% have a final diagnosis. D-Dimers test, ultrasound, Doppler ultrasound, computed-tomography (CT), magnetic resonance (MR) or venography, are the most important support methods of the diagnosis.[11]
The American Thoracic society and the society of Thoracic Radiology have proposed an algorithm for the diagnosis of pulmonary embolism. This algorithm included CT pulmonary angiography, ventilation-perfusion scintigraphy, MR angiography and intravascular pulmonary angiography. [11]
The review of the societies guidelines about thromboembolism prophylaxis (The American Congress of Obstetricians and Gynecologists, 2015; The American College of Chest Physicians, 2015 and The Royal College of Obstetricians and Gynecologists, 2015) shows that there is a significant difference between each others guidelines, but, even with an amount of studies conducted, they concluded that the thromboembolism risk during delivery has increased in the last years. They justify it with an inadequate risk assessment, inadequate thromboprophylaxis, failure to investigate symptoms, and failure to ensure multidisciplinary care. [12] [13]

In cases of sudden death, if the autopsy is performed, it is necessary to check thrombus in the main pulmonary arteries to confirm the diagnostic of pulmonary thromboembolism. It is also important to confirm that the embolism was the cause of death and not a postmortem event. [8]
Then it is required the research of the thrombus origin which is made by dissecting the deep veins of the legs and the pelvic veins. [8]

Hypertensive syndromes remain the leading causes of maternal morbidity and mortality. These syndromes have pathological consequences in the normal liver function. [14]
The hypertension-related liver disease during pregnancy includes pre-eclampsia (PE), eclampsia (E), heamolysis, elevated liver enzymes, low platelets syndrome (HELLP) and acute fatty liver of pregnancy (AFLP). [14]

1.2) Preeclampsia and eclampsia

Pre-eclampsia (PE) is an hypertensive syndrome characterized by hypertension (>140/90mmHg) plus proteinuria (upper urinary excretion to 0.3g of protein in a 24-hour urine sample) after the 20th week.[8]
PE can be allocated into two categories, early and late PE. Although the etiology of this pathology is yet unknown, the main hypothesis in early PE cases is an alteration on the normal implantation of the placenta [8] which includes the presence of an incomplete and imperfect invasion of the spiral arteries into the trophoblast during the implantation. [15] [16] [17]
The later PE is related with an enlarged placental mass or surface. It can occur in cases of pregnant women with diabetes, nulliparous pregnant, anemia or in high altitudes. [17]
The hypertension has major systemic repercussions, the most important of which is in the cardiovascular (increased in blood pressure and in cardiac output) and in hematological system (risk of hypovolemic shock, thrombocytopenia and disseminated intravascular coagulopathy (DIC)). [15] Placental abruption, HELLP syndrome, thromboembolism and pulmonary edema, are some examples of the complications caused by hypertension progress. [18]

Eclampsia (E) is an evolution of PE, with major neurologic changes like convulsions and coma, when other causes, such as epilepsy, are excluded. [8]
Hypertensive syndromes (PE, E, HELLP syndrome) affect 2-8% of the pregnant women. Nulliparous pregnant, extreme age groups and family history have an higher risk of developing PE. Higher risks are also associated with systemic lupus, diabetes and chronic hypertension.[6]

Typical signs and symptoms of hypertensive syndromes are: headache, epigastric pain, visual alterations, oliguria or anuria, hepatocellular dysfunction and hyperreflexia.[16]
During pregnancy, the diagnosis can be done by periodically measuring the blood pressure and the proteinuria (screened with 24-hours urine test).[8] The symptomatology, the presence of high blood pressure (140/90 mmHg) [11] and upper urinary excretion to 0.3g of protein in a 24-hour urine sample, make the diagnosis of pre-eclampsia. [8] Nowadays, some studies about the substitution of 24-hours urine collection for the 12-hours test show an advantage of convenience and improved clinical efficiency (of the later). Furthermore, there are investigations in order to implement some biomarkers in the first and second semesters to prevent this syndrome from de beginning. For the first semester it is proposed Placental Growth Factor (PIGF) and in the second semester the Human Chorionic Gonadotrophin ([hCG]>2.0 MoM) and Associated Plasma Protein-A ([PAPPA]<5th centile). These biomarkers seem to have more accuracy to predict pre-eclampsia. The importance of these new biomarkers is the need for early start of tracing PE. Nowadays this prevention only starts in the mid to the end of the second trimester and the dysfunction of the placenta may already be establish. [17] [19]
The large discordance between the cutoff of the different studies is the greatest obstacle to the progress in prevention and early diagnosis of hypertensive syndromes.[17]

PE kills 3 women per day, this remains as one of the most frequent causes of death in pregnant women. In the case of sudden death the main findings at autopsy are a soft liver parenchyma with associated hematoma or a large haemoperitoneum caused by the liver capsule's rupture especially the right lobe (liver rupture).[7] The microscopic section shows edematous changes in fibrinoid material, and recent blood extravasation.[8] A third of the cadavers present brain alterations, with subcortical edema, vascular lesion consistent with fibrinoid necrosis of arterial walls, perivascular infarction and hemorrhage within the white matter, basal ganglia and pons or even a ventricular rupture can be present.[11]

1.3) HELLP syndrome

The HELLP syndrome is characterized by hemolysis (consequent of a microangiopathic hemolytic anemia (MAHA)), elevated liver enzymes and decreased platelet concentration ($<100.10^9$/L). [20]

This syndrome is classified as a severe variant of the PE and it occurs in about 5 to 10% of pregnant women with severe PE [8] with a frequency of 0,2-0,6% during pregnancy.[14] The peak of incidence is between 27 and 37 weeks and until 48 hours after delivery.[20] Contrary to PE, the risk factors are multiparous pregnant women, caucasian and older than 35 years old women.[16] In a posterior pregnancy the risk of recurrence is 20%. [20]

The main symptom of HELLP syndrome is an upper right quadrant pain or epigastric pain, that worsens overnight and can be associated with nauseas and vomiting. These symptoms usually progress continuously but the intensity can change spontaneously. [20]
The diagnosis include laboratory analysis with platelets count under $<100.10^9$/L and an increased concentration of liver enzymes (AST, ALAT). The last analysis, often reflects the presence of hemolytic processes. Although the increased levels of α-GST and GST-a1 are the most sensitive factors to appoint acute liver injury, they cannot be used in diagnosis yet. [20]
HELLP syndrome have a maternal mortality of 3,4-24,2 %. [21] The autopsy findings are similar to preeclampsia. [8]

1.4) Acute fatty liver of pregnancy

Although still poorly elucidated, the main hypothesis to explain this condition is the deficiency of the long-chain 3-hydroxyl-CoA dehydrogenase. [8] This alteration interferes in the fatty acid degradation through beta oxidation in hepatic mitochondria. [14]

Acute fatty liver of pregnancy is a potentially fatal condition but it is very rare with an incidence of 1 per 10000 pregnant women. [3, 8, 14, 16] It occurs most frequently in the third trimester and the differential diagnosis with other hypertensive syndromes can be difficult. [16]

The first symptoms related with this pathology are headache, nausea, vomiting, abdominal or focalized right upper quadrant pain, itching and confusion, which lead the pregnant women to the hospital. [11]
The diagnosis is difficult and normally the first diagnostic hypothesis are PE or hepatitis. Although biopsy is rarely done due to the large risk to the pregnancy, it is the only way to confirm the diagnosis. Imagiological exams like ultrasound and magnetic resonance have low sensibility. That's why the presumed diagnosis is done by the clinical and laboratory findings (elevation in the transaminase, direct bilirubin, and uric acid levels, anemia normocytic normochromic and leukocytosis)[16]

The major complications and causes of death in pregnant women, with acute fatty liver, are renal failure, DIC and sepsis. [16] At autopsy, it is possible to check a fatty liver[8] The diagnosis is microscopically confirmed with the presence of microvascular centrilobular steatosis, cholestasis, cytoplasmic ballooning, inflammation and necrosis of hepatocytes. [8]

Obstetrical hemorrhage continues along with infections and hypertension to constitute the famous triad responsible for the majority of cases of death in pregnant women. The decreasing maternal mortality rate related with hemorrhagic causes has as been achieved in recent years and that represents a great global maternal mortalities decrease.

1.5) Hemorrhage

1.5.1) Hemorrhagic stroke

Hemorrhagic stroke (HS) incidence has been increasing lately. It is subdivided in subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH). The SAH results, more frequently (approximately 80%), from a cerebrovascular alteration or a saccular aneurysm rupture. [11, 22] In a lower percentage, SAH can be a consequence of a coagulopathy, angiopathy, venous thrombosis, infection, drug abuse, cancer or trauma. [11] The ICH is caused by a rupture of a small vessel previously damage by chronic hypertension. [11]
Although a stroke is uncommon during pregnancy or the postpartum period, a venous infarction thrombosis of dural sinuses can cause it. It has a multifactorial etiology including hypercoagulable state typical of pregnancy, protein S deficiency and dehydration. [8]

HS has a prevalence of 6 per 100000 deliveries.[22]The advanced age (above 35 years old), arterial hypertension, pregnant woman medicated with anticoagulants, antiplatelet and fibrinolytic drugs, alcoholism and the presence of arteriovenous malformations are the major risk factors recognized. [8] During the postpartum period the risk of SAH increase.[8]

The major symptoms and signs are headache, vomiting and local neurologic deficits. [8] The diagnosis of this condition implies a large index of suspicion by the clinician. A lot of pregnant women enters the emergency service with few classic risk factors of HS or only with a slight increase of the blood pressure.[22] Imagiologic exams after suspicious clinical findings are the best way to determine the diagnosis of SAH.[8]

The mortality percentage of SAH and ICH are 10% and 20% respectively.[22] At autopsy it is possible to evaluate the presence of hematoma. Microscopic section may present vascular malformations or other vascular disease, infection findings, cancer and other possible etiologies. [8] The autopsy can confirm the presence of thrombosis in the dural sinuses.[8]

1.5.2) Haemoperitoneum

Facing haemoperitoneum the clinician should consider a uterine rupture, ruptured subcapsular hematoma, aneurysm rupture of the splenic artery, ectopic pregnancy, placenta previa, placenta increate and abruption placentae. [8]

a) Ectopic pregnancy

Ectopic pregnancy is the implantation of the blastocyst outside the endometrial lining of the uterine cavity. This occurs in consequence of the anatomic or functional obstruction, impair tubular motility, ciliary dysfunction and molecular chemotactic factors that stimulates and protects tubular implantation. [23]
Although this is a rare cause of maternal death, is still the primordial cause in the first trimester due to hemorrhage and infection, with a prevalence of 20 per 1000 pregnancies. [16]
The most frequent location is in the fallopian tubes (98%). [8] [16]
Genital and pelvic infections are risk factors of ectopic pregnancy, as the use of medically assisted reproduction techniques, tobacco, scar of previous surgery and age above 35 years old. [16]

A pregnant woman may have an acute or subacute symptomatology. The most common presentation is a woman with a menstrual delay, positive pregnant test, abdominal-pelvic pain, metrorrhagia and hypovolemic shock. [8] More than 50% of the pregnant women with ectopic pregnant have at least a risk factor. [23]

The diagnosis of this pathology includes reunion of clinical findings, transvaginal ultrasound and B-HCG (>1000IU/L) dosing. [23] If the diagnosis is not clear, an exploratory laparoscopy can be done. [8]
A tubal ectopic pregnancy location can result in tubal abortion, tubal rupture or spontaneous resolution.[15]

At autopsy it's possible to observe the ectopic localization and the haemoperitoneum in case of rupture. [8]

b) Uterine rupture

The uterine rupture (UR) is a disruption of the uterine wall that can be total or partial. [8] UR can be traumatic or non-traumatic.
UR has a prevalence of 1 per 100 deliveries to 1 per 1850 deliveries.[8] In non-traumatic cases, the risk factors are previous caesarean section, increased gestational age, multiparity and the use of uterotonic drugs (like oxytocin and prostaglandins). Uterine rupture can occur during an obstetric intervention as mid-forceps delivery and prolonged labor with cephalopelvic disruption. [8] The traumatic uterine rupture is due, in most of the cases, to road accidents. [8]

In the beginning of pregnancy, women may have an acute abdomen frame with intense pain and signs of internal bleeding. With the advance of pregnancy, the patient may be asymptomatic or only presenting a slight abdominal pain or vaginal bleeding. During labor, the rupture is felt with a strong localized pain in the abdomen. [16]
The diagnosis is based on clinical history and physical examination. In case of doubt, it is possible to resort to an ultrasound to confirm the diagnosis. [16]

In the autopsy it's possible to observe the haemoperitoneum and the rupture of the uterine wall. [8]

c) Placenta implantations

The placental previa (PP) is defined as a low implantation of the placenta that obstruct totally or partially the internal os. Low-lying placenta is defined as a low implantation localized at least two centimeters of the internal os. [11]
PP is an important cause of bleeding during the 3th trimester of pregnancy and delivery. This pathology has a prevalence of 3 to 5 per 1000 deliveries. [24] [20] The major risk factors are multifetal gestation, age above 35 years old, previous cesarean section, cigarette smoking and an increase in perinatal screening of maternal serum Alfa- fetoprotein. [11]
The most typical and frequent sign is a moderate painless vaginal bleeding. [11]
The diagnosis is made by ultrasound or MR, allowing verification of the placenta position. [16]
In the autopsy it's possible to confirm the wrong position of the placenta. [8]

The excessive invasion of the myometrium by the placenta is called accreta. Different degrees of invasion have different classifications (accrete, increte, precreta). The accrete placenta is the main cause of intractable postpartum hemorrhage and emergency hysterectomy intrapartum. [24]
The defect of the decidua with an imperfect fibrinoid or Nitabuch layer and the alteration of cytotrophoblasts, that can control the decidua invasion through the control of angiogenesis and growth factors, represent the major alteration in this pathology. [11]
The incidence of accretism is 1 per 533 deliveries. Throughout time it was discovered a correlation between increte placenta and placenta previa, previous uterine curettage, previous cesarean section, multiparity and advanced maternal age (above 35 years-old).[24]
Typically, pregnant women resort to emergency service with vaginal hemorrhage that may

appear only in the third trimester. [11]
Although the diagnosis can be made by Doppler ultrasonography and MR imaging, when a pregnant woman is asymptomatic (absence of vaginal bleeding) these tests are less sensitive.[24]
The accrete placenta represents 8% of the deaths related with hemorrhage. In autopsy, the anatomopathologic diagnosis of accretism is made by histological study with the presence of trophoblastic islands in myometrium. [8]

The abrupt placenta (AP) is the separation, total or partial, of the placenta from the local of implantation. AP begins with hemorrhage to the decidua that then split, leaving a thin layer adherent to the myometrium. The etiology can be an impaired trophoblastic invasion with subsequent atherosis. Other possibility can be inflammation or infection of the myometrium.[11]
The prevalence is 4 to 35 per 1000 deliveries.[25] AP can be a cause of dangerous bleeding in addition to the risk of intrauterine death.[20, 24] This injury can be caused by a traumatic event or it may have a non-traumatic cause like maternal hypertension, cigarette smoking and cocaine abuse.[8]
The main symptoms and signs are abdominal pain and abdominal tenderness. The shock can manifest within few minutes or hours after the injury .[8, 24]
The diagnosis is based on clinical history and physical examination and supported by some imaging tests such as ultrasound and MR.[8, 25] In the initial phase pregnant women can be asymptomatic, if there isn't more abruption of the placenta, the diagnosis can only be made after delivery when assessing the placenta, when the clinician verifies an area few centimeters wide with a dark surface and with blood clots. [11]
At autopsy, the placenta must be verified in order to find signals of abruption like dark surface and the presence of blood clots. The presence of cocaine in the blood and the presence of signs of trauma should be analyzed too. [8]

d) Ruptured aneurysm of the splenic artery

The ruptured aneurysm of the splenic artery is more common in the third trimester of pregnancy and this pathology has an high mortality rate. The main causes are unknown, but the main hypotheses are hemodynamic and hormonal (increase in the estrogens and progesterone concentrations) alteration during pregnancy, uterus compression and the increase in the arteries flow. [26]
The increase in estrogens and progesterone concentration can have as consequence the disruption of the internal elastic lamina, fragmentation of the elastic fibers, degeneration of smooth muscle fibers, and failure of elastin formation. The relaxation can be increased too and that may affect the elasticity of the splenic artery wall. [26]
The majority of this aneurysms are saccular, located 2-5 cm from the splenic hilum. [8] The prevalence is between 0,01 and 10,4 %. The multiparity, portal hypertension, atherosclerosis and medial fibrodisplasy increase the risk of this pathology. [26]

Pregnant females who have this condition may be asymptomatic (when the aneurysm has less than 2 cm in the major diameter or they can present an epigastric pain with or without signs of shock. [27] The diagnosis has improved recently due to the evolution and use of imaging studies as angiography, the MR and CT.[27]

The mortality of the ruptured aneurysm of the splenic artery is around 75%. [28] At the autopsy, it can be very difficult to identify the aneurysm. It is important to careful dissect the full length of the splenic artery. [8]

Amniotic fluid embolism (AFE) is a rare cause of sudden death in pregnant women, but, it is considered by many, as a key factor. [29] Mortality has decreased by raising awareness as a condition that can become catastrophic. [29]

1.6) Amniotic fluid embolism

Despite the lack of information, it is thought that the main cause of AFE is related to immunology, where an idiosyncratic reaction is triggered by the access of amniotic fluid to the maternal circulation. This access implies failure in the physical barriers in utero-placental unit (e.g. Endocervical veins). [29] Recurrence risk is very low.[29] The coagulopathy occurs as a result of both procoagulant and anticoagulant factors and it's likely to be multifactorial. [29]

The incidence, 7 to 8 per 100000 births, is still somewhat vague due to the different types of methodology used in studies and the low number of studies. [29] [8] [30]
The major risk factors are the changes in the barriers (e.g., placental abruption) or increased intrauterine pressure (e.g., uterine contractions), maternal age above 35 years old, multiple pregnancy, cesarean section, assisted delivery or eclampsia. [29]

Clinical signs related with AFE are hypotension, fetal distress, pulmonary edema or ARDS, cardiopulmonary arrest, cyanosis and coagulopathy. However, the clinical presentation usually has a great diversity of sings and symptoms.[29]
Diagnosis is based on four inclusion criteria (1) the acute hypotension or cardiac arrest; (2) acute hypoxia; (3) severe coagulopathy with clinical bleeding in the absence of other explanations; (4) an event during delivery, cesarean delivery, surgery to the uterus or within a period of postpartum and defined by no other explanation for the results. [29] Imaging study can give some contribution to the diagnosis, but there is no specific test.[29]
The diagnostic can be achieved by demonstrating the presence of squamous cells of the fetus in maternal blood, through the introduction of a catheter into the pulmonary artery. [8]
Clinical suspicion, traditional laboratory data, or intravascular cellular debris (demonstrated only in 50% of patients) are insufficient to make a definitive diagnosis of AFE. Nowadays, biomarkers capable to confirm the diagnosis are inexistent. Modern biomarkers may help differentiate AFE from other conditions.[30]
The highest levels of STN (Sialyl Tn), an fetal antigen present in meconium and amniotic fluid, which is an high sensitivity test used, were found in AFE non-survivors and can be the key for predicting the severity and mortality of AFE. [29]

The main consequences of this pathology are heart failure and DIC. [31] In cases of sudden death it's hard to find the failure of the barrier. [8] The autopsy diagnosis is made by histological studies with the detection of fetal products in the maternal pulmonary arteries, like squamous epithelial cell, meconium, lanugo and mucins (origin in the intestinal tract of the fetus). The difference between fetal cells and maternal squamous cell shedding is made by the presence of nuclei in the maternal peeling endothelial cells, which normally does not appear in fetal squamous cells. [8] We can still do immunohistochemical staining with cytokeratin that mark the squamous cells but not the endothelial ones. Mucins are usually present but it is hard to detect because they rarely stain with routine dyes. However it's possible to stain with "Alcian blue" or mucins staining. It is sometimes possible to find products of amniotic fluid in the uterine and cervical veins. [8]

Sepsis remains a leading cause of maternal death, in contrast with what was expected, the maternal sepsis has increased even in developed countries. [32]

1.7) Sepsis

Nowadays the main scientific societies have different definitions for the classification of sepsis. This fact makes the compression of this pathology even harder. [32]
WHO, in 1992, defined puerperal sepsis as an infection of the genital tract occurring at any time between the rupture of membranes or labour and the 42 days in the postpartum period. Two or more of the following symptoms are present: pelvic pain, fever, abnormal vaginal discharge and delay in the reduction of the size of the uterus. [33]
ICD-10 (International Classification of Diseases) defines puerperal sepsis as an higher temperature of 38°C continued for 24h or recurrent during the period between the end of the first day and the end of the tenth day after birth. [32]
In 2002, a surviving sepsis campaign defined systemic inflammatory response syndrome (SIRS) as a widespread inflammatory process caused by an infection, trauma, thermic lesion or sterile inflammatory process. It requires the presence of two of the criteria: (a) temperature <36ºC or >38º C, (b) frequency cardiac >90 bpm, (c) respiratory frequency>20cpm and (d) leukocytes <4 $x10^{10}$ cells per liter or> 12x 10^{9} cells per liter.[7]
The surviving sepsis campaign defined sepsis as a SRIS associated with an infection. [32]
Severe sepsis presents hypotension and hypoperfusion, which responds to fluid resuscitation, and organ dysfunction. And finally septic shock is the worst state of sepsis without fluid resuscitation response[7].
Sepsis may have an obstetric or non-obstetric etiology. Obstetric causes include septic abortion, chorioamnionitis, perineal infection, endometritis, surgical wound infection and puerperal mastitis. The non-obstetric causes included urinary infection, respiratory infection, appendicitis, pancreatitis, hepatitis, malaria and infection by the human immunodeficiency virus (HIV), among others. [32]
Between all this causes, pyelonephritis, chorioamnionitis and endometritis are the most important causes of septic shock in pregnancy and postpartum period. [32]

An american study, conducted between 1998 and 2008, showed a sepsis incidence of 1 per 17246 births. The most frequent risk factors depend on the infection agent, host factors and pregnancy and delivery factors.[32]
Anemia, obesity, previous caesarean section, premature rupture of membranes, diabetes mellitus or glucose intolerance, immunosuppression, tobacco, maternal age above 35 years old, chronic diseases and low socio-economic stratum are included in the host factors. [32]
The main agents related with maternal death are streptococcus group A beta-hemolytic and *Escherichia coli*. The first agent exists in 5-30% of the population as an asymptomatic way. [7]

The main clinical findings are fever or hypothermia, tachycardia, tachypnea, hypoxia, hypotension, oliguria and state of consciousness. [32] The diagnostic is done by the clinical findings, a blood culture and C-reactive protein. The signals and symptoms can be subtle due to the physiological adaptation of the pregnancy. [32]
Blood cultures should be made in the source of infection such as vaginal, respiratory secrecies or cerebrospinal fluid before the introduction of antibiotics. Imaging scan like chest x-ray, ultrasound and computer tomography may help the diagnosis.[7]

Sepsis in pregnant women can result in increased preterm birth rate, hypoxia, acidosis, stillbirth and fetal infections.[34]
Puerperal sepsis has worldwide mortality of 15%. The recent increase in maternal deaths in developed countries can be justified with (a) the advanced maternal age, obesity, cardiovascular disease, chronic renal diseases, erythematosus systemic lupus and smoking; (b) household childbirth; (c) increased number of infections by Streptococcus beta Group A beta-hemolytic and Escherichia coli; (d) the use of assisted reproductive techniques, invasive prenatal diagnostic test, and caesarean delivery [32]. An antibiotic prophylaxis can reduce the incidence of sepsis and, consequently, the incidence of maternal deaths. [32]

Sepsis rarely is the primary diagnosis. Normally the objective of the autopsy is to demonstrate a concomitant disease, which may have been neglected. The best interval to do the autopsy is in the first 15 hours after death and the acquisition of some clinical information is fundamental before starting the post-mortem exam. [35]
Sampling may change from situation to situation but the more extensive and varied it is, the possibility to do the diagnosis and determine the starting point of the infection increases. [35]
Examples include sampling of blood, organs product aspiration, cerebrospinal fluid, urine and feces. The culture of these products is still very effective, however, nowadays other exams including DNA technique like PCR supported by immunohistochemistry can facilitate the diagnosis. [35]

2) Maternal deaths indirectly related to pregnancy

Maternal deaths indirectly related to pregnancy include all deaths caused by the intensification of a disease that already existed prior to pregnancy.[7]
The cardiac diseases are causing more deaths in recent years. It includes some examples like peripartum cardiomyopathy, aortic dissection, arrhythmogenic right ventricular cardiomyopathy among others. Central Nervous System (CNS) disorders most frequent are intracerebral hemorrhage, cerebral thrombosis and epilepsy.[7]
Also included respiratory diseases (e.g. asthma), endocrine, metabolic and immunologic diseases (e.g. diabetes), gastrointestinal system diseases (e.g. pancreatitis), blood disorders (e.g. thrombotic microangiopathy), circulatory system diseases, kidney and tumors (e.g. pheochromocytoma).[7]
The HIV or bacterial infections prior to pregnancy are also indirect causes. [7]

2.1Cardiac disease

The cardiac disease in pregnant women may be one of the main indirect causes of sudden death. [7] This pathology has a prevalence of 2,31 per 100000 pregnancies.[7] The main risk factors are obesity, tobacco and hypertension.[7]
The etiology can be congenital (pulmonary hypertension and cardiac congenital diseases) or acquired (ischemic and non-ischemic). [7]
The acquired non-ischemic conditions include the aortic dissection, peripartum cardiomyopathy, myocarditis, arrythmogenic right ventricular cardiomyopathy, among others.[8] [7]

2.1.1) Peripartum cardiomyopathy

Peripartum cardiomyopathy (PC) etiology, like most of the disorders during pregnancy, is still under research.[8] The main hypothesis for PC is a fetal autoimmunity and microchimenism, myocarditis and the dietary excess of salt or deficiency of selenium. PC is marked by the development of systolic heart failure.[36]
PC can have an hereditary and genetic component.[36] The most recent studies propose a truncating variants as a strong genetic predisposition. [36]
This cardiomyopathy it's more frequent in the last month of pregnancy until 6 months after birth, with the peak of incidence in the second month after delivery.[8]
The incidence of this pathology is 1 per 1000 or 4000 births.[8] [36] PC is more frequent in black pregnant women, age above 35 years old, multiparous, preeclampsia and hypertension.[7]

Pregnant women with this condition usually present dyspnea, edema, orthopnea, tachypnea

and tachycardia.[7] The diagnosis is made with a chest x-ray and an echocardiogram. They should be accompanied by a specialist and possibly included in the regional transplant center.[7] In US, PC represents 4% of all cardiac transplants. [36]

PC has a mortality of 5 to 10%, and it is a rare cause of maternal sudden death. [36] The most frequent mechanisms of death are attributed to arrhythmia or thromboembolism. [8] At autopsy there are nonspecific findings as enlarge heart, dilated cardiomyopathy, irregular myofibrils and fibrosis, and variable myocardium T cell infiltration. [7][7] [8]

2.1.2) Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited disease in which 50% of the cases with autosomal dominant transmission. ARVC is characterized by fibro-fatty changes of the right ventricle, ventricular arrhythmia, and sudden death.[37]
Although this ARVC is normally considered a pathology of desmosomes, in fact only 50% of the cases have mutations in the genes of this component. Recent studies in mice showed changes in signaling via Rho-kinase, which is implicated in the regulation of intracellular transport and cytoskeletal filament organization, that supports the desmosomal complex proteins in cell-cell junctions in the myocardium. Mice that had Rho-kinase inhibition exhibited spontaneously developments of cardiac dilatation and dysfunction, fibro-fatty change and ventricular arrhythmia that resulted in premature death of the mice. This pattern corresponds with ARVC in humans. [37]
Ventricular tachycardia is provoked by hemodynamic changes of pregnancy, as the increased in the cardiac output or anemia when associated with prior cardiac pathology.[38] [39]
This pathology has an incidence of 1:5000 births.[38]

This disease has a ranging spectrum of presentation, from asymptomatic to sudden death. Usually pregnant woman presents with palpitations and syncope. The diagnosis is made by electrocardiogram, classically with a left bundle-branch block that can be accompanied by inversion of the T wave from V1 to V3 and premature ventricular complexes. [38] Nowadays the availability of genetics tests increases the early recognition of ARVD.[38]

In the autopsy it's possible to evaluate the fibrous-adipocyte tissue replacement myocardium, although it is not pathognomonic. Normally there is attenuation of myocytes, transversal stretch marks and areas with less myofibrils, this alteration gives the appearance of "bubbly". [40]

2.1.3) Aortic dissection

Acute aortic dissection (AAD) is a rare phenomenon during pregnancy despite a well-established risk relationship. [41] AAD is characterized by a rupture of the intimal layer of the aorta with blood extravasation, forming a subintimal hematoma that produces a false double-channel effect. [41] It has an incidence of 1,39 cases per 100,000 person/year among pregnant women under 40, compared to 0.4 cases per 100,000 person/year in pregnant women aged between 15 and 45. [41] [7] As previously mentioned, pregnancy is a risk factor, which is increased with gestational hypertension, preeclampsia, Marfan and Ehlers-Danlos syndrome.

Pregnant women with sudden and persistent thoracic and interscapular pain should lead to an AAD diagnosis that can be done by Trans-esophageal echocardiography, a CT scan or an MRI. [7] [41]

AAD can complicate with aortic valve insufficiency, avulsion of the carotid arteries resulting in myocardial infarction or stroke. [41] This pathology represents 3-14% of maternal cardiac death. [41]

In autopsy it is possible to observe hemothorax and a rupture of the aortic or coronary artery.[8] Microscopically it's possible to confirm the recent artery dissection with the underlying aortic medial degeneration. Because Marfan and Ehlers-Danlos syndromes are both great enhancers of aortic dissection as in global population as in pregnant women, genetic testing for these syndromes should be done. [41] [7]

2.1.4) Cardiac ischemia and myocardial infarction

Nowadays, myocardial infarction is one of the most frequent causes of pregnant cardiac death (20%). The etiology can be variable like atherosclerosis, coronary dissection, or even an autoimmune disease.[7]
In more than 25% of the cases the main etiology is coronary dissection, most frequent in the left descendent anterior artery, in the anterior wall (78%).[42] The coronary dissection is more frequent in the postpartum period and it is possibly a result of the hemodynamic and hormonal changes during pregnancy. In young pregnant women the most frequent etiology is embolic and normally with classic risk factors but with the presence of structural cardiac diseases.[42]
Coronary spasm and dissection can be consequent of drug abuse (e.g. cocaine). [42]
The prevalence of cardiac ischemia (CI) is 6.2 per 100.000 pregnancies [43] CI is more frequent during the third trimester and six weeks following the deliver. [43]The risks factors are obesity, tobacco, age above 35 years old, more than 3 births, diabetes, hypertension, thrombophilia and family story. [7] [43] Pregnancy increases three or four times the risk of a CI.[43]In pregnant women, and because the etiology is rarely atherosclerosis, the symptoms can be very different. The most frequent ones are abdominal or epigastric pain associated by vomiting and dizziness. [7]

The diagnosis is made by a serial of parameters that include the symptomatology, electrocardiogram (ECG) and the study of the cardiac enzymes (like troponin). A normal ECG does not exclude the diagnosis. In order to overtake this problem, women should do various ECG. The study of coronary arteries is also necessary trough a coronary angiogram with angioplasty with or without stenting. [7]

At autopsy it is possible to evaluate the typical macroscopic and histological changes of a myocardial infarction and also explore the etiology. In the majority of the cases, it's possible to find atheroma plaques in the coronary arteries or a dissection of the same arteries.[7]

2.2) CNS (central nervous system)

2.2.1) Epilepsy

Sudden death in epilepsy (SUDEP) is defined, in pregnant population as in general population, as: "*death, unexpected, witnessed or unwitnessed, non-traumatic and without the patient drowning due to epilepsy, with or without evidence of a seizure and excluding the documented epilepticus status, where autopsy did not reveal a toxicological or anatomical cause of death.*" [44]
The physiologic alteration during the pregnancy, such as the increase in the progesterone and estrogen and the alteration in the absorption, distribution, metabolism and elimination of the antiepileptic drugs, is the main hypothesis for the negative impact of epilepsy. [45]
In many countries such as the UK, studies have concluded that the mortality rate increases 10 times during pregnancy in women with epilepsy when compared to women without the disease.[44] The prevalence of epilepsy in pregnancy is 0.61 to 1 per 100,000 births. [7] The major risk factors of SUDEP in a pregnant woman are chronic epilepsy with poorly controlled seizures, hyperventilation, sleep privation, stress, physical pain and lack of compliance with

medication.[46]

Sometimes it is difficult to diagnose epilepsy during pregnancy due to the proximity of clinic sings typical of pregnancy. Headaches, changes in mood, dizziness, confusion and memory loss are some of the most common symptoms.[46] The diagnosis of epilepsy is mainly clinical but there are auxiliary diagnostic tests such as EEG, CT and MR that can help.[47]
Guidelines recommend to prevent SUDEP *(a) choose the optimal treatment before conception, (b) prefer monotherapeutic approach if possible, (c) opt for the most efficient AED according to the type and frequency of seizures, (d) begin with the lowest effective dose, and (e) not forget folic acid supplementation*. [45]

In autopsy of SUDEP cases it's possible to find alterations in several organs including (a) brain (edema and hypoxia signs), (b) heart (fibrosis driver system), (c) lungs (increased weight and pulmonary edema with alveolar hemorrhage and exudate) and finally the (d) liver (increased venous congestion and weight which are cardiac failure signals).[48]

2.3) Blood flow

2.3.1) Thrombotic microangiopathy

Thrombotic microangiopathy include primary disease like thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome.[8]
TTP characterized by the presence of microthrombi rich in vWF and the presence of ADAMTS13 inhibitors in the blood. [49] Normally, it arises before of 24 weeks.
The prevalence of this pathology is 1 per 25000 to 1 per 100000 pregnancies. [50]

Most frequent symptoms and signs are neurological (lethargy, seizures, mental confusion), fever, kidney dysfunction, severe thrombocytopenia (gingival, gastrointestinal or genital bleedings, bruises, petechial), abdominal pain, diarrhea, anemia, intravascular hemolysis, visual disturbance and cardiac dysfunction by thrombotic events in the microcirculation.[16]
In the case of pregnant women who have already TTP prior the pregnancy it's normal the worsening of the situation. Unfortunately, in many cases it is necessary to terminate pregnancy before fetal viability.[16]

The absence of pathognomonic laboratory data hampers the diagnosis. Identification of ADAMTS-13 deficiency is helpful to allow specific care of this potentially fatal disease. When the diagnosis is done in postpartum period, the maternal prognosis is reserved. [16]
Lactic deshidrogenase (LDH) is always very high due to hemolysis. [16]

TTP is a disease with a mortality rate higher than 60% when untreated and although it is not a specific disease of pregnancy, this pathology can be trigger by it. [49] In cases of sudden death, at autopsy the conditions that cause the formation of widespread microthrombi are called thrombotic microangiopathy of pregnancy. [8]

2.4) Tumors

2.4.1) Pheochromocytoma

Pheochromocytoma is a cromaphin tissue tumor located, in 80-85% of cases, in the adrenal glands and, in 15-20% of the cases, in extra-adrenal sites (for example Zuckerkandl body) characterized by increased release of catecholamines. [51] [52] This tumor typically known as "10% tumor" because it is 10% bilateral, 10% multiple, 10% hereditary and 10%

malignant.[51]
It is extremely rare in pregnant women, with an incidence of 1 per 50,000 pregnancies. [51]

Clinically the main symptoms are headache, hypertension, hyperhidrosis, and heart palpitations.[51] [52]
In pregnant women, despite the absence of screening tests, it is recommended to carry out biochemical tests, measurements in blood and urine catecholamine metabolites levels (metanephrine and Normetanephrine) when in presence of a sustained or paroxysmal hypertension, clinical signs of increased secretion of catecholamines or when they have a family history of pheochromocytoma. [51] [52]
When biochemical tests have positive results, the second phase of diagnosis is achieved by undertaking imaging tests to locate the tumor. [51]

The risk of sudden death in pregnant women with pheochromocytoma is due to paroxysmal hypertension and hypotension that may be precipitated by vaginal delivery, the fetal movements, abdominal palpation, uterine contraction, bleeding or general anesthesia.[52]
Vaginal delivery has been contraindicated in the past but is acceptable nowadays if the patient is stable. [52]
The mechanism of death normally is necrosis of the tumor produced by the compression of the gravitic uterus that leads to a cardiopulmonary failure by the extensive liberation of catecholamines.[51]
At autopsy it's possible to find a mass in the adrenal gland that it is formed in the medulla layer. [51, 53] Macroscopic analysis demonstrate a necrotic and hemorrhagic mass. In microscopic analysis it's possible to confirm the endocrine origin with the presence of polygonal cell with low number of granules and acidophilic cytoplasm, decentered nucleus fusiform and round elements that suggest anisocytoses, as well the disposition of the cell over rows conjunctive and vascular tissue with an anarchic orientation.[51]

Discussion and conclusions

Sudden death in pregnancy has a major impact in the society, but actually in Portugal, as in many other countries, it has been poorly explored.

In 2007, DGS published a report about the main causes of maternal mortality. Although these datas have more than 8 years, these were the last numbers presented in Portugal. [54] This publication includes maternal mortality (MM) (figure 1), ratio of maternal mortality (RMM) (Table 1), the maternal death by age groups (Table 2) and the main causes of maternal mortality (Table 3). [54]
The most frequent causes are cardiac disease such as, pulmonary hypertension, cardiac congenital disease, aortic dissection, peripartum cardiomyopathy, myocarditis, right ventricular arrhythmogenic cardiomyopathy, and ischemic disease. [7, 54] A percentage of 21,7% of the maternal death had unknown cause. [54]

In 2015, DGS publish a report with the most important health index, whose maternal mortality was included. This report show the datas of 2013, with a maternal mortality of 8 deaths per 100000 live births.[5]

The last data publish by the WHO, in 2015, indicated that Maternal Mortalities are 12 and 239 per 100000 live births in developed and developing countries respectivel.[2] With this data we can concluded that Portugal is below of the mean of the developed countries, even so, the importance of the reduction of this numbers is crucial.

Nowadays knowledge, allows the prevention of the majority of deaths, but failures in diverse points turn it not a reality yet. Failure to detect signs or symptoms and the late feature of the

pregnant women to medical cares are actually the two most important causes of maternal death. [55] [56] Although it is important to review the services provided to every pregnant, it is also important understand the various barriers that stand between pregnant woman and these services. The difficulty in transport to medical facilities, low educational level and economic problems are some of the obstacles for the preventive measures come evenly to all pregnant women.[57]
Since all pregnant women, and especially those who have high risk from the beginning, are at risk of suffering complications that can lead to her death, it is important to implement measures that allow uniform access to maternal health care from the start and more intense in the third trimester as we already been mentioned, is the time when the risk of death increases.[55]

The production of more recent reports that specifically show the current numbers of each cause of maternal death and the number of case that the etiology remained unknown is actually very important to understand the reality of our country in order to actualized our guidelines in the routine of the pregnancy vigilance and to create better access to the health care for the pregnant woman. So, to complete this reports it's very important that each case is study individually and, in the end, all cases have a definitive diagnosis of the cause of death. The diagnosis can be made by the clinical with de clinic symptoms, sings and auxiliary test. If the clinician has doubts about the pathology, it is possible to accomplish a clinic autopsy. On the other hand, if there are some clinical doubts it's necessary to perform a medical legal autopsy. The pos-mortem study should be standardized in order to avoid misclassification and loss of information.[7] A study based on anatomo-pathological findings is a good possibility to better understand the real weight of each cause of maternal deaths around the world.

During the research, we realized that the majority of the diseases that appear during pregnancy are still understudied, the few scientific studies that have so far been allowed in pregnant women were not enough to understand the etiology, pathogenesis and even to test some therapeutic specifically in this stage of woman's life. Only in some diseases, like hypertension syndromes, hemorrhage and infection, there is a well-established prevention methodology. Surviving sepsis campaign, as others campaigns, had a good impact in death reduction in non-pregnant women due to establishing guidelines, standardized treatment and greater investment in training of health professionals. Perhaps it is time to apply this strategy to pregnant women.

In order to compare the situation of Portugal with other European countries, we researched their respective reports and we realize that, like Portugal they weren't updated for many years. [58] [59] A Swedish study shows a pregnancy related mortality ratio of 7.3 which is 64% highest than the report of World Health Organization.[58] But just as Portugal, the Swedish report is from 2007. [58]
The Spaniards report includes statistic numbers between 2001 and 2005 show a RMM of 4.1 and a increase in 20% of the number of pregnant woman with 35 years or over since 1996. [59]

United Nations created, in 2000, the Millennium Development Goals (MDGs), which include maternal death surveillance and response (MDSR) in order to improve the precision of the notification of the deaths. The aim of MDSR is to get less than 30 deaths per 100000 pregnancies until 2030. [1]

In each hour, 30 women die around the world from pregnancy complications. Some of maternal death can be avoided with better individual heath cares so it is very important to prioritize the health politics and funding programs to achieve better data on maternal mortality and thus improve the health indices.[55]

Although it still has a long way to go, MRSD studies are the beginning for a new era with a more accurate view of this major problem that is maternal mortality. Review on this subject

allows saving the lives of many pregnant women and their newborns.

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ANO	MM	NV	RMM
1993	10	114030	8,8
1994	12	109287	11,0
1995	9	107184	8,41
1996	8	110363	7,2
1997	14	113047	12,4
1998	6	113510	5,3
1999	6	116038	5,2
2000	3	120071	2,5
2001	15	112825	13,3
2002	15	114456	13,1
2003	10	112589	8,9
2004	15	109356	13,7
2005	6	109457	5,5
2006	20	105514	19,0
2007	11	102567	10,7

Table 1. Number of maternal deaths (MM), live births (NV) and MMR between 1993 and 2007 in Portugal (adapted from Directorate-General of Health) [54]

AGE	2001	2002	2003	2004	2005	2006	2007	TOTAL	%
15-19				1	1	1	1	4	4,3
20-24	2	1	2	1				6	6,5
25-29	2	4	2	3		4	1	16	17,4
30-34	2	6	5	4	3	9	2	31	33,7
35-39	6	3		3	2	5	7	26	28,3
40-44	2	1	1	2		1		7	7,6
>44	1			1				2	2,2
TOTAL	**15**	**15**	**10**	**15**	**6**	**20**	**11**	**92**	**100,0**

Table 2- Maternal mortality by age group between 2001 and 2007 (adapted from Directorate-General of Health) [54]

Causes of maternal death	2001	2002	2003	2004	2005	2006	2007	TOTAL	% Of total of known causes
Direct								52	72,2
Haemorrhage/ coagulopathy	6	1	1	2	2	4	3	19	26,4
Hypertensive syndrome of pregnancy	3	4	2			7	1	17	23,6
Infection/ sepsis	1		1	3		1	1	7	9,7
Tromboembolis		1	1		3		1	6	8,3
Others embolis					1	1	1	3	4,2
Indirect								18	25,0
Infection		1	1		2		4		5,6
Cardiac death	2	1	1	1		1		6	8,3
Cancer	1	1						2	2,8
CNS		1				1		2	2,8
Others		1		1		2		4	5,6
Accidental/ incidental								2	2,8
Accidental/suicide				1			1		2,8
Complete with known causes	13	11	7	8	6	19	8	72	100,0
Unknown	2	4	3	7		1	3	20	21,7
TOTAL	15	15	10	15	6	20	11	92	

Table 3- Causes of maternal death between 2001 and 2007(adapted from Directorate-General of Health) [54]

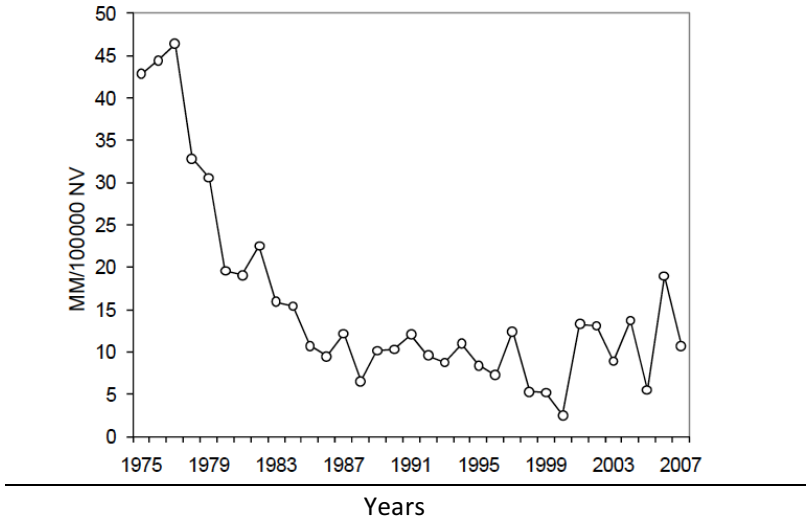

Figure 1. Evolution of MMR, number of maternal deaths per 100,000 live births between 1975 and 2007(adapted from Directorate-General of Health) [54]

MDG region	MMR	Range of MMR uncertainty (80% UI)		Number of maternal deaths	Lifetime risk of maternal death 1 in:
		Lower	Upper		
World	216	207	249	303000	180
Developed regions	12	11	14	1700	4900
Developing regions	239	229	275	302000	150
Northern africa	70	56	92	3100	450
Sub-saharan africa	546	511	652	201000	36
Easten asia	27	23	33	4800	2300
Eastern asia excluding china	43	24	86	378	1500
Southern asia	176	153	216	66000	210
Southern asia excluding india	180	147	249	21000	190
South- eastern asia	110	95	142	13000	380
Western asia	91	73	125	4700	360
Caucasus and central asia	33	27	45	610	1100
Latin america and the caribbean	67	64	77	7300	670
Latin america	60	57	66	6600	760
Caribbean	175	130	265	1300	250
Oceania	187	95	381	500	150

Table 4- estimates of maternal mortality ratio(MMR, maternal deaths per 100000 live births), number of matenal deaths, and lifetime risk, by National Millennium Development Goal (MDG) region, 2015(adapted from WHO) [2]

Agradecimentos

A realização desta monografia contou com importantes apoios e incentivos sem os quais não se teria tornado uma realidade e aos quais estarei eternamente grata.

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Anexos

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AUTHOR INFORMATION PACK

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