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Risk factors for intrauterine deaths in the third trimester of pregnancy. A holistic approach of case series and literature review

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Abstract

Objectives: There is a plethora of references in the international bibliography regarding correlation of various risk factors and intrauterine death in the third trimester, such as gestational diabetes mellitus, preeclampsia, endometrial infections as well as endometrial growth restriction. The purpose of the present study is to analyze demographic and socio-economic factors to draw conclusions on improving health services for pregnant women.

Methods: 41 cases of intrauterine deaths, after 28 weeks of pregnancy, were studied retrospectively from the archives of the 1st Department of Obstetrics and Gynecology Alexandra Hospital, during a 3-year period (2015-2018). The risk factors assessed, were the age, the race (White/Caucasian, Ethnic, Asian, and Black), the socio-economic status, smoking, body mass index (BMI), educational level, gestational age, monitoring (or lack) of the pregnancy, and pathology observed during the pregnancy though.

Results: The average age of women was 31 years old, the average body mass index (BMI) was 27.4, while most of them were White-Caucasian (75,6 %) The majority of women had a low educational and socio-economic level, 68,3 % (28/41) and 61% (25/41) respectively. On top of that, 14/41 (34.1 %) were smokers, the mean age of gestation was the 32 weeks of pregnancy, and the fetal gender was female (63.41%). The gestational preeclampsia was found to be the most important factor for intrauterine death and most of the women had not monitoring during the pregnancy (61%).

Conclusions: Interpretation of the results showed that low educational level and low socio-economic level were independent risk factors for endometrial third trimester deaths. On the contrary preeclampsia was the leading cause of death.

Key Words: Low socio-economic level, intrauterine death, stillbirth

Introduction

Fetal death occurring later in pregnancy (stillbirth) is generally classified separately from fetal death earlier in pregnancy (miscarriage). Stillbirths are a major public health issue and a sensitive marker of the quality of care around pregnancy. The definition of stillbirth is the delivery of a baby in the perinatal period which fails to show any signs of life. As is well known, the International Classification of Diseases (ICD) and the World Health Organization (WHO) recommendations are now widely recognized and used for reporting of stillbirth rates.

The WHO and the ICD define fetal death as “death prior to the complete expulsion or extraction from its mother of a product of conception irrespective of the duration of pregnancy. It is essential to know the gestational age or weight or length of embryo. For international comparison, the WHO defines stillbirth as a baby born dead at 28 weeks of gestation or more, or with a birthweight of ≥ 1000 g, or a body length of ≥ 35 cm¹. A cut-off based on gestational age is more appropriate than birthweight as a predictor of maturity and hence viability². Every year, an estimated 2.6 million stillbirths occur worldwide, most of which are thought to result from preventable causes. About 98% of all stillbirths occur in Low-Income Countries and Middle-Income Countries³.

The causes of fetal death are complex as there are many contributing and interacting factors. In developed countries, the most prevalent risk factors associated with stillbirth are non-Hispanic black race, nulliparity, advanced maternal age, obesity, preexisting diabetes, chronic hypertension, smoking,

alcohol use, achieving pregnancy using assisted reproductive technology, multiple gestation, male fetal sex, unmarried status, and past obstetric history⁴. Thus, it may be difficult to assign a definite cause to a stillbirth. A significant proportion of stillbirths remains unexplained even after a thorough evaluation.

Apart from the immediate distress of losing a baby, stillbirth has been reported to have severe psychosocial consequences for parents, including anxiety, long-term depression, post-traumatic stress disorder and stigmatization³. Couples who have experienced a stillbirth need to understand why it happened and want to know the risk for future pregnancies.

The aim of this report is to understand the causes of stillbirth and to study demographic and socioeconomic factors in addition to the factors stated above, in order to draw conclusions for the improvement of health services for pregnant women.

Statistical analysis

This study was a case series performed at the 1st Department of Obstetrics and Gynecology of Alexandra Hospital in Greece. This is a retrospective study conducted between 2015-2018 and includes 41 intrauterine deaths after 28 weeks of pregnancy from the archives of the hospital. Variables analyzed in this study include age, race (White/Caucasian, Ethnic, Asian, and Black), socio-economic status, smoking, body mass index (BMI), educational level, gestational age, monitoring (or absence of it) during the pregnancy, and pathologies observed during gestation.

The average age of women was 31 years old, the

average body mass index (BMI) was 27.4, while most of them were White-Caucasian (75,6 %). The majority of women had a low educational and socio-economic level, 68,3 % (28/41) and 61% (25/41) respectively. On top of that, 14/41 (34.1 %) were smokers, and the mean age of gestation was the 32 weeks of pregnancy, and the fetal gender was female (63.41%). The gestational preeclampsia was found to be the most important factor for intrauterine death and most of women had not monitoring during pregnancy (61%).

Discussion

Stillbirth is one of the most common adverse pregnancy outcomes, occurring in 1 in 160 deliveries in the United States⁴. There are plenty of causes associated with intrauterine death, such as maternal age, pathologies in pregnancy, lifestyle, and demographic socio-economic factors. Special mention should be made that the etiology of intrauterine deaths differs between high-income (HIC) and low-middle income countries (LMIC). Countries such as Asia, sub-Saharan Africa, Southeast Asian and Latin America belong to the low and middle- income countries⁵.

Nearly 98% of all stillbirths occur in LMIC, primarily in low-resource settings⁶. The main causes of stillbirth in these countries are infection, fetal asphyxia, trauma, congenital abnormalities, fetal-maternal hemorrhage, prolonged labor, fetal distress, congenital infections, underlined maternal medical conditions, the lack of a skilled attendant for delivery, low socio-economic status, poor nutrition, previous stillbirths and advanced maternal age significantly contributed to stillbirths^{7,8}. In developed countries are more often related to congenital abnormalities and factors such as obesity, smoking and maternal age over 47⁹. Within both high and low-resource settings, several common risk factors for stillbirths have been documented. The incidence of stillbirth reported from western countries ranges from 4.7% to 12.0%¹⁰.

Advanced Maternal age

Stillbirths are more likely to occur among those women who are of advanced age. In HIC, the proportion of women giving birth over the age of 35 has increased over time, giving rise to concern about the impact of advanced maternal age on pregnancy outcomes. In contrast, women in LMIC have their first birth before 35 years old. In comparison to the evidence surrounding earlier pregnancy loss, the association between stillbirth and advanced maternal age is harder to interpret. Some large population-based registries and systematic reviews have consistently demonstrated a modest increase in stillbirth risk with advanced maternal age, with the over 40 group being at a higher risk than women aged 35-39. However, Samantha C. et colleagues, shows the risk increases along with increasing maternal age¹¹. Furthermore, maternal age is found to significantly increase the frequency of adverse pregnancy outcomes including fetal growth restriction, preeclampsia, and placental abruption¹².

Pathology of pregnancy

Over 5% of stillbirths are caused by conditions such as congenital anomalies, placental malfunction, preeclampsia/eclampsia, and abruption¹³. Preeclampsia is associated with intrauterine death and the risk of it clearly increases with advancing maternal age, especially for women whose age is >40 years old¹⁴. In LMICs, eclampsia is much more prevalent in pregnant women than in high-income settings, but the main barrier for prevention of eclampsia is timely access to effective antenatal care and magnesium sulphate. Optimizing the place of care and tailored management will depend on the healthcare setting and severity of disease¹⁵. Other risk factors associated with preeclampsia include antiphospholipid antibody syndrome, history of pre-eclampsia in previous pregnancy, chronic hypertension, pre-gestational diabetes, and BMI >30. Obesity is one of the leading

factors contributing to the overall burden of disease worldwide. Although advanced maternal age is associated with increased risk of obesity and acquired medical disorders, such as diabetes, infertility, the use of reproductive technologies, and multiple gestations, it is also an important independent risk factor for stillbirth¹⁶. Population based studies showed the risk with increasing maternal body mass index (BMI) to be 2 to 14 times higher than in normal weight women, depending on the severity of obesity and the gestational age of pregnancy. Women with the aforementioned characteristics must be closely monitored¹⁷⁻¹⁹.

Smoking and Alcohol

Maternal smoking during pregnancy has several adverse health effects on both the mother and the child, including congenital birth defects, ectopic pregnancy, preterm delivery and low birth weight²⁰. In many developed countries, the rates of smoking in pregnancy have been declining over recent decades with current prevalence estimates between 10% – 19%. Smoking in pregnancy in developed countries tends to be higher among women who have low income and poor education²¹.

In addition, a strong association between maternal smoking during pregnancy and stillbirth has been reported²². Takawira C Marufu²⁰ et colleagues showed that women who smoke during pregnancy have a 47% increased risk of stillbirth and that the risk of stillbirth is more at higher levels of cigarette consumption. Also, Sarah M. Bjørnholt et colleagues found that the risk of stillbirth was further increased by increasing numbers of cigarettes smoked per day during pregnancy; however, women who stopped smoking at the beginning of pregnancy reduced their risk of stillbirth to that of non-smoking women²³.

Although associations have been found for maternal drinking during pregnancy and abortion, being small for gestational age, and stillbirth, the associa-

tion with stillbirth may be limited to binge drinking. Many of the detrimental effects of prenatal alcohol exposure may depend on the achieved maternal and fetal blood alcohol concentration and duration of exposure. Women who continue to drink alcohol after they know they are pregnant, especially in large amounts, including binge drinking, may increase the risk of fetal death, and clinicians need to pay special attention to these women²⁴.

The study of Hein Odendaal et colleagues report that combined drinking and smoking after the first trimester of pregnancy compared with no exposure or quitting before the end of the first trimester were associated with the risk of late stillbirth. The association between stillbirth and combined prenatal exposures to drinking and smoking is important given the extensive documentation that alcohol is frequently used in combination with tobacco cigarettes, including by pregnant women²².

Fetal gender

The male disadvantage persists from early stages of conception, throughout gestation and delivery and into adulthood. Male babies are at a 10% higher risk of stillbirth than female babies³. It is known that a range of adverse pregnancy outcomes are more common in males than females, and there are sex-specific differences in the growth and function of male and female placentae²⁵. The probable mechanisms include X-linked congenital conditions, increased risk of preterm labour, and poor fetal growth for male babies. The latter two disorders might be related to a higher incidence of placental vascular conditions, including pre-eclampsia³.

In addition, it is known that differences in male and female development begin very early in life. For example, Y chromosome-linked genes are transcribed at the two-cell stage, and, in animal models, male embryos have faster development and higher metabolic rates than females potentially leaving the

male fetus more vulnerable to a range of stressors, including endocrine fluctuations, oxidative stress, and nutritional compromise. In our study, the predominant fetal gender was the female. On the other hand, Eran Hadar and colleagues showed that the stillbirth rate of 0.14%, with a higher proportion of female stillborn and they found that placental abruption affects significantly more male stillborn. This finding contradicts the universal notion of an intrauterine male disadvantage²⁶.

Low socioeconomic profile

In addition, the low socioeconomic profile which includes education, type of work, income criteria and marital status of the pregnant woman was shown to be a strong parameter associated with increased rate of intrauterine deaths. Single, divorced, or widowed women were at increased risk of stillbirth. For women who live in LIC, stillbirth rates are ten to 20-fold higher than those rates seen in HIC⁸. Women who live in LIC have lower socioeconomic profile than women who live in HIC²⁷.

The maternal socio-economic and maternal risk factors for stillbirth observed were similar to those documented in low-middle income country studies conducted elsewhere. Elizabeth M McClure and colleagues, in one of the largest prospective population-based studies of stillbirth in low-resource, report that women without formal education were also more likely to deliver stillbirths (RR 1.9, 95% CI 1.7, 2.2), compared to those with higher education. Likewise, much research carried out in Nepal, Ethiopia, Tanzania, Pakistan, Nigeria, Yemen, and India reported that less-educated women and decreased antenatal visits were more likely resulted into stillbirths^{6,7,28-33}.

Similarly, those women having less access to antenatal care, as documented through fewer medical visits and reduced rates of prenatal testing, had increased risk for stillbirth⁶. Also, women with no

formal education or just primary education know that they do not have a chance at a white-collar job and so they start early to learn a skill or trade that will make them self-employed hence they become economically more empowered than their counterparts with secondary education who keep hoping for white-collar job which they rarely get³⁴.

This association may exist because educated mothers are more conscious about maternal health, the importance of a balanced diet, and the need for medical visits, and may be more likely to be aware of unhealthy behaviors like smoking and alcohol drinking³⁵. According to a study conducted in north-east Tanzania, low paternal education was strongly associated with stillbirth³⁶.

Among the individual-level factors, the spatial analysis in Ethiopia, showed that being Catholic and Protestant religious followers was significantly associated with lower odds of stillbirth compared with being Orthodox religious followers. This might be related to the misperception of religious followers towards maternal healthcare service utilization as religion shapes their reproductive health decision making and practices and thereby governs women's desire to use maternal health services. Moreover, Orthodox religious followers consider women who give birth at home are blessed and using contraceptives is a sin. Also, women do not expose their body to health professionals during delivery³⁴.

It seems that the maternal occupation is significantly associated with the prevalence of stillbirth among mothers. Nonye E Anyichie³⁷ and colleagues via a study conducted in 2019 showed that unemployed women and housewives had the highest prevalence of stillbirth within the study period. Employment is associated with financial empowerment; women who are gainfully engaged can afford to decide to use skilled attendant during antenatal and delivery period thus reducing their chances of having a stillbirth.

Healthcare facilities and medical follow-up

On the other side, stillbirth in LIC is related with healthcare facilities, for example the poor equipment for intrapartum monitoring, and the late monitoring of pregnancy. Poor monitoring and care during pregnancy is another poor prognostic factor leading to an increased rate of intrauterine deaths. Differences in the ability to access good quality obstetric services may be due to differences in maternal employment status; for example, a pregnant woman with no occupation may not afford the cost of health services which may later result to home delivery³⁷. This might be because in developing countries maternal health services were not available and reachable, particularly caesarean section is done at tertiary hospitals. For example, in East Africa, the majority of the population are rural residents and hospitals are not accessible due to transportation problems which resulting not saving the fetus's life because the caesarean section is not done at the right time³⁸. Caesarean section is done to save the life of newborns from high-risk pregnancies. Only health posts and health centers are relatively accessible, and women are too far to avail of services from hospitals where caesarean section is offered. Furthermore, having no antenatal care visit had a significant association with increased stillbirth, and this was consistent with previous findings in low-income to middle-income countries³⁴. That is also reflected in our study where the rates were highest amongst the unsupervised deliveries.

There are two large studies, which support that there is a difference in distribution and range of causal factors contributing to stillbirth between LIC and HIC. The factors that independently associated with stillbirth in LIC were late booking visit after 12 weeks, preeclampsia and placental abruption. The maternal education and counselling play pivotal roles in the understanding of pregnancy warning associated with adverse outcomes such as stillbirth, the importance of antenatal care^{3,37,39}.

Risk of recurrent stillbirth

Also, the risk of stillbirth in subsequent pregnancies is higher in women who experience a stillbirth in their first pregnancy. According to Kathleen Lamont and colleagues, women who experienced a stillbirth in the past have a fivefold increase in the odds of stillbirth in a subsequent pregnancy. In conclusion, for many stillbirths it is difficult to determine the exact cause, and according to classification systems for informing and establishing the likely cause for the loss of the baby these are classified as unexplained. Because of the considerable number of classification systems currently in use, the proportion of stillbirths classified as unexplained varies widely, from 9.5% to 50.2%⁴⁰.

Conclusion

To sum up, the etiology of intrauterine death is multifactorial, and knowledge of the causes is very important for proper management of women associated with an increased risk of stillbirth. More research is necessary to identify the exact causes of stillbirths in LIC, as well as the proper combination of interventions necessary to significantly reduce their current number.

Due to the scale of the problem, creating a functioning prenatal and obstetric care system that will ensure access to all pregnant women globally should be our ultimate goal, in order to close the socioeconomic gap that prevents women in LIC from getting the expert maternal care they need.

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