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Research Article

Recurring Materno-fetal Complications in Late Pregnancy: An Integrative Review

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Abstract

Background: pregnancies at advanced ages are increasingly common in society, which represents a concern for the health system, since they are associated with complications and different comorbidities during pregnancy, which can negatively impact its course, due to the occurrence of adverse maternal-fetal events. Therefore, this study aims to summarize the main complications of advanced maternal age and their repercussions.

Methods: an integrative review was developed, using the LILACS, MEDLINE, and PubMed databases and the search formula: ("complications") AND ("pregnancy") AND ("maternal age"), including articles in Portuguese, English, and Spanish from 2018 to 2023, excluding duplicates and review articles.

Results: 484 articles were filtered and, after applying the inclusion and exclusion criteria, 28 articles were selected to compose the study. From them, a higher incidence of gestational diabetes mellitus was evidenced in mothers over 35 years of age due to the progressive depletion of pancreatic β-cell function. In addition, pre-eclampsia was found to be seven times more common in pregnant women aged 40 years than in those under 30 years of age, as the gastro-omental arteries reduce compliance, affecting blood pressure regulation.

Conclusion: Therefore, advancing age is related to the emergence of metabolic alterations and cardiovascular diseases that can harm maternal and fetal health, since pregnant women over 35 years of age are more prone to comorbidities that can result in adverse maternal and neonatal outcomes.

Abbreviations

AMA: Advanced Maternal Age; FGR: Fetal Growth Restriction; GDM: Gestational Diabetes Mellitus; PE: Pre-eclampsia; PPH: Postpartum Hemorrhage

Introduction

Advanced Maternal Age (AMA) is characterized by a pregnant woman who is 35 years of age or older at the time of birth [1,2]. Therefore, the choice for a late pregnancy involves

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factors such as access to birth control resources and infertility treatments, the prioritization of a professional career, and financial stability, which are reasons that have strengthened in recent decades and that explain the postponement of pregnancy [3,4].

However, many studies indicate that women over 35 years of age are more prone to different comorbidities, such as obesity, diabetes, and hypertension, which can negatively impact the course of pregnancy [5,6]. As a result, pregnancy among women with advanced maternal age has been associated with adverse maternal and neonatal outcomes, such as Pre-Eclampsia (PE), Gestational Diabetes Mellitus (GDM), Postpartum Hemorrhage (PPH), Fetal Growth Restriction (FGR), placental abruption and premature birth [7,8].

It is worth mentioning that a very common complication in late pregnancy is gestational hypertension, defined as blood pressure levels from 140/90 mmHg without proteinuria, which can progress to pre-eclampsia if proteinuria is added, both after the 20th week of gestation [9,10]. This complication becomes prevalent in advanced ages due to low levels of nitric oxide and high oxidative stress that can arise with aging, which can compromise the relaxation of the endothelium, associated with increased cardiac output during pregnancy [11].

Another recurrent complication in pregnancy at an advanced age is diabetes, which is explained by vascular endothelial damage that tends to increase with advancing age, in addition to increased insulin resistance and deterioration in the function of pancreatic β cells also associated with AMA [12,13].

It is worth adding that pregnant women over 35 years of age tend to have adverse perinatal outcomes such as premature birth, low birth weight children, and perinatal mortality compared to those under 30 years of age [13,14]. Such complications do not yet have sufficient explanations in the literature, but they may be associated with the vascular pathology of a placenta in an elderly pregnant woman and progesterone deficiency that tends to decrease with increasing age [15].

Therefore, taking into account the different adverse outcomes that a late pregnancy can cause in the perinatal period, it is important to summarize the main complications associated with advanced maternal age and the repercussions that these scenarios can have for the pregnant woman and the child.

Methods

The study is characterized as an integrative review in which bibliographical works on a given subject are analyzed and synthesized to provide a relevant theoretical framework, in addition to discussing new perspectives on a specific topic [16]. Therefore, the authors relied on the PICO strategy (Population, Intervention, Control, and Outcomes/Outcome) to formulate the research question, which resulted in: "What are the recurrent maternal-fetal complications in late pregnancies?".

The search was carried out in August and November of 2023, in the PubMed, LILACS, and MEDLINE databases. The keywords used for the search were provided by the Health Sciences Descriptors (DeCS) and, with Boolean operators, resulted in the following search formula: ("complications") AND ("pregnancy") AND ("maternal age"), with a filter for Portuguese, English and Spanish languages and articles from 2018 to 2023. Initially, the studies were selected by title, abstract, and full text, in that order. The exclusion criteria were review articles, duplicate studies, studies involving animals, and studies that, after being read in full, did not answer the research question.

Using the search criteria, 484 articles were filtered, excluding reviews, studies involving pregnant women under 35 years of age, multiple pregnancies or procedures, as well as studies involving animals and, after full reading, 28 articles were selected to compose the state of the art. Therefore, each study was analyzed, regarding the theoretical foundation and the general characteristics of the studies, highlighting the most relevant points to be synthesized in the current study.

Results

Association of GDM with advanced maternal age

Gestational Diabetes Mellitus is a condition in which women without a previous diagnosis of diabetes experience chronic hyperglycemia during pregnancy. In women with advanced maternal age, it can signal the risk of complications capable of negatively impacting the course and outcome of pregnancy [17]. In this regard, it is important to take into account that the incidence of GDM increases linearly with maternal age, reaching a peak Around 40 years of age, this association still needs to be studied further, but it is believed that the etiology may be based on progressive vascular endothelial damage in advanced age [5].

Some studies indicate that the first pregnancy promotes adaptations of the hemodynamic system, being able to reduce vascular resistance, thus reducing constrictive cytokines, which leads to a reduction in the risk of maternal complications in subsequent pregnancies. As a result, it was observed that primiparous mothers with AMA were 2 to 3 times more likely to develop GDM, especially in the 35 to 39 age group [18].

Furthermore, it is important to highlight that it is stated in the literature that the greater risk of developing GDM with advancing age is due to the progressive depletion of the function of pancreatic β cells, which leads to reduced sensitivity to insulin [19], and lower serum levels of adiponectin [20] and the increase in the level of serum lipids, which also contribute to the development of the condition [17]. Therefore, universal cautious screening in all pregnant women over 35 years of age is extremely important, given that glycated hemoglobin levels above 7% in the first trimester are associated with more unfavorable birth outcomes [6].

Studies show that, as GDM is a complication that increases with age, increased attention is justifiable, especially from the

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third trimester of pregnancy, with the increased frequency of medical consultations, ultrasound, and fetal monitoring [21]. This must be done, since patients with GDM present fetal complications that include congenital malformations most commonly related to the cardiovascular system. Furthermore, in cases of obese pregnant women, there is a 68% chance of not being able to have a vaginal birth, and practically double the chance of having multiple complications during pregnancy compared to healthy patients [22].

Moreover, in a retrospective cohort study using data from the Dutch National Perinatal Registry (Perined), primigravidae and multigravidae over 40 years of age had twice the risk of gestational disorders, including gestational diabetes, for women over 45 years the risk was almost tripled [23]. As a result, it is understood that the most significant risk factors for gestational DM are advanced age, excess weight before or during pregnancy, diabetes in the family, and GDM in a previous pregnancy [24].

Then, it is important to emphasize that not only is the obstetric population aging, but women are also less healthy. According to a study using a classic epidemiological approach with data from the National Center for Health Statistics (NCHS) in the United States, it was possible to observe higher rates of pre-existing diseases and those associated with pregnancy in elderly women, for example, in 2014, women above 45-year-olds were 2,7 times more likely to develop chronic hypertension than women under 35 [25].

From this perspective, it is believed that maternal neuroendocrine and inflammatory processes are factors that can influence pregnancy outcomes. In this way, a good lifestyle can contribute to ensuring a healthy internal environment, reducing the risk of maternal complications, especially GDM, as it can be controlled by self-regulated behavior compared to other complications [18].

Repercussions of pre-eclampsia in late pregnancy

Pre-eclampsia is an idiopathic disease that can occur and develop rapidly during pregnancy, leading to serious damage to the function of some maternal viscera, such as the liver, kidneys, and blood clotting system or fetal complications, in addition, in more severe cases, can lead to the death of the maternal-fetal binomial [26].

This pathology is characterized by increased blood pressure levels (hypertension) accompanied by the presence of high protein concentrations in the urine (proteinuria), generally detected for the first time after the 20th week of pregnancy [11,19]. This complication in pregnant women of advanced age is of extreme concern, as it significantly increases the probability of adverse events for the maternal-fetal binomial in both the short and long term during pregnancy and is the main cause of maternal and perinatal death, representing 14% of total maternal deaths [27,28].

In this sense, according to the retrospective cohort study by Kahveci, et al. [17], the risks of pre-eclampsia and gestational hypertension were 3 times higher in pregnancies with maternal age over 35 years compared to control groups below that age [8]. This result corroborates the research by Shan, et al. [18], in which the risk of pre-eclampsia was 7 times higher in the group formed by pregnant women over 40 years old than in the group with pregnant women under 30 years old, [18] and with the population-based retrospective cohort study of Wu, et al. [29], which demonstrates twice the risk of pre-eclampsia in pregnant women aged 43 years or over, compared to patients under 35 years of age.

Based on this principle, preeclampsia is associated with several factors behind the high mortality rate in pregnant women and newborns, especially in cases of advanced age. This occurs due to the incidence of adverse perinatal and neonatal outcomes in both the short and long term, such as eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count), neonatal respiratory distress syndrome and neonatal thrombocytopenia, since PE interferes with the number of platelets in both maternal and fetal and neonatal circulation [27].

Therefore, the reason for the incidence of pre-eclampsia in late pregnancies is due to increased weight and oxidative stress resulting from advanced maternal age, since women over 35 are more prone to obesity, which leads to an amount excessive adipose tissue and the release of adipokines/cytokines that lead to chronic inflammation and several other metabolic disorders [11]. Furthermore, oxidative stress is a phenomenon that tends to increase with advancing age, which can worsen the risk of adverse outcomes in pregnancy, such as pre-eclampsia, as it is related to the increased production of oxidizing agents and a simultaneous reduction in the efficiency of antioxidant systems [30].

Furthermore, it was discovered that advanced maternal age affects the structure of the gastro-omental arteries in pregnant women, resulting in a reduction in the compliance of these systemic vessels that contribute to the regulation of blood pressure, thus, cardiovascular complications in pregnancy, such as pre-eclampsia, occur more frequently in pregnant women of advanced maternal age [24].

Because of this, health professionals need to be careful with the development of pre-eclampsia in pregnant women of advanced age. To achieve this, complete maternal care, adequate cardiovascular preventive strategies and monitoring of maternal-fetal vital signs are necessary to ensure that neonatal anomalies do not occur and to try to stabilize them to prolong the pregnancy until the fetus reaches a greater gestational age [24]. Furthermore, there is evidence of aspirin prescription as a way to mitigate the adverse neonatal sequelae associated with pre-eclampsia [23].

Other complications associated with advanced maternal age

The association between AMA and obstetric complications is currently being studied extensively, since late pregnancy is related to some problems during pregnancy, such as an increased risk of unplanned cesarean section among nulliparous

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women. This increased risk was corroborated by a study that demonstrated a higher incidence of unscheduled cesarean section in women over 40 years of age, as 26.01% of women in the advanced maternal age group had an unscheduled cesarean section, while 15.26% (95% confidence interval, 14.28-16.29; n = 769) of women in the non-advanced maternal age group underwent the procedure [7].

Given this, a pertinent analysis was carried out in a study that considered progressive complications according to age, based on the comparison of pregnant women under 35 years old, between 35 and 40 years old, and over 40 years old. In this sense, respectively for the aforementioned groups, the percentages of women who underwent labor induction were 25.2%, 28.4%, and 34.3%, and, concerning unscheduled cesarean section, they were 18.2%, 24.1%, and 29.3% [31]. Furthermore, there is a four- to seven-fold increased risk of spontaneous preterm birth associated with advancing maternal age [19].

In line with this, cesarean section is one of the most common perinatal outcomes, especially in women over 35 years of age, reaching 50.5% of analyzed cases of women over 40 years of age. This increasing age-related rate of cesarean sections may have an association with the natural age-related weakening of the myometrium, a lower amount of oxytocin receptors, a lower clinical threshold for obstetric interventions, and increased rates of maternal systemic diseases and obstetric complications [17].

Regarding other possible complications associated with AMA, in a descriptive study that compared pregnant women under 45 years old and pregnant women over 45 years old, that is, very advanced maternal age, it was concluded that, in the case of late pregnancies, there was a greater rate of postpartum hemorrhage among women aged 45 to 54 years, in a context of higher relative risk (aRR, 3.46, 95% CI, 3.15-3.80) [32].

Furthermore, it was observed that pregnant women over 45 years of age have 20% higher rates of placenta previa and double the chance of placental abruption than the group below this age group [20]. In this context, placental abruption can be defined as the complication in which the placenta separates prematurely from the uterus, and placenta previa may be related to the lodging of the placenta close to the internal cervical os [17].

Another aspect was exposed by a retrospective cohort study, which revealed a higher prevalence of premature births among women over the age of 40, with advanced age being an independent risk factor (OR 1.36 95% CI 1.16 - 1.61, $p < 0.05$) [18]. According to analysis results, the rates of perinatal outcomes such as spontaneous preterm birth before 34 weeks of gestation and spontaneous late preterm birth between 34 and 37 weeks of gestation increased with maternal age [17].

Discussion

Nowadays, due to changes in lifestyle and socioeconomic factors, women are choosing to delay pregnancy [4,33]. However, with advancing age and a new lifestyle, the emergence of metabolic and cardiovascular diseases are inherent risk factors for pregnancy, as the body gradually loses the ability to perform its functions. As a result, adverse perinatal outcomes occur more frequently in pregnant women with AMA [29].

Given the global trend toward delaying pregnancy, the increased likelihood of advanced maternal age influencing adverse perinatal outcomes is a concern that has steadily increased in recent years [17]. Thus, it is possible to understand that complications in pregnancy such as gestational diabetes mellitus, pre-eclampsia, and other complications are more common and present more risks among patients with AMA [31].

After analyzing the studies, it was possible to note that they point to the physiological changes of increasing age, the consequences of aging itself, as the cause of the higher incidence of gestational diabetes in AMA. Furthermore, pre-existing diseases cannot explain all the associated adverse events to advanced age, therefore, when analyzing only low-risk pregnant women, they still found worse results in the AMA group [32].

In this scenario, studies indicate that the occurrence of gestational diabetes in the obstetric population increases concomitantly with increasing age, being six times higher in women aged 40 years or older compared to women aged 20 to 29 years [31].

Moreover, pre-eclampsia, recognized as a risk factor for future cardiovascular diseases, is also a much more frequent pathology in women with AMA [33]. This complication is responsible for a high mortality rate in pregnant women of advanced age, in addition to reflecting on several adverse outcomes for the maternal-fetal binomial, both in the short and long term [34].

As a result, pre-eclampsia must be identified by healthcare providers so that the implementation of monitoring, full follow-up and education, and appropriate cardiovascular preventive strategies are carried out in an attempt to mitigate maternal-fetal harm [35].

Regarding other possible outcomes, several studies consider that AMA is a strong indication for cesarean delivery [36,37]. It was also found that the delay in the beginning of the first phase of labor is related to the pregnant woman's age, especially in primiparous women, which indicates that oxytocin should be administered during the dilation period [29,30].

Furthermore, very clear causes for the association of advancing maternal age with an increased risk of spontaneous premature birth have not yet been established, but placental vascular pathology may be one of the mechanisms involved [17]. Another possible predisposing factor for premature birth in older women is progesterone deficiency since premature birth is associated with low levels of this hormone. Therefore, progesterone supplementation is important, as it is effective in preventing this problem [19].

Regarding the growing trend of postpartum hemorrhage, the rates were higher in the age group over 40 years old. This

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risk requires attention, as PPH, despite being, in most cases, preventable or treatable, remains one of the main causes of maternal death [19,38].

Several factors influence the phenomenon of increasing maternal age, including changes in social customs, improvements in women's professional and educational prospects, and the spread and greater access to contraception [19].

In this panorama, maternal age is considered a risk factor for several diseases and unfavorable obstetric outcomes. Therefore, amid the current and progressive trend of increasing this type of pregnancy, knowledge of obstetric risks is of fundamental importance, which allows the health team to properly guide pregnant women, to provide relevant care and prevention during the pregnancy prenatal [39-41].

Conclusion

It is concluded that, with advancing age, some physiological functions of the maternal organism undergo changes, such as an increase in the production of oxidizing agents and a reduction in the functioning of antioxidant systems, characterizing the high presence of oxidative stress resulting from aging. In addition to these, other factors, such as progressive damage caused to the vascular endothelium, increased insulin resistance, and weight gain resulting from advanced age, make it easier for older women to present and accumulate different comorbidities or adverse repercussions, before and during pregnancy, which can bring several harms to the health of the maternal-fetal binomial.

Due to these factors, from this study, it was observed that some complications are more recurrent in late pregnancies, namely: gestational diabetes mellitus and pre-eclampsia, followed by postpartum hemorrhage, placental abruption, and premature births. Therefore, complications associated with AMA must be better correlated with advancing age during obstetric consultations and follow-ups in a way that can be understood, to increase monitoring and preventive strategies, thus mitigating adverse repercussions.

Authors' contribution

Cainã Araújo Saraiva, Bianca Braga Gomes, Luana Azevedo Dourado, and Sandriny Maria de Almeida Oliveira: Conception, data curation, formal analysis, investigation, methodology, validation, visualization, writing - original draft, writing - review and editing

Sávio Benvindo Ferreira: Conception, writing - review and editing, and approval of the final manuscript.

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