Determinants of preterm birth: proposal for a hierarchical theoretical model

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Abstract Preterm birth (PB) is a syndrome resulting from a complex relationship between multiple factors which do not have fully understood relationships and causality. This article discusses a hierarchical theoretical model of PB determinants, considering maternal characteristics such as sociodemographic, psychosocial, nutritional, behavioral and biological aspects, traditionally associated with increased risk of PB. The variables were distributed in six dimensions within three hierarchical levels (distal, intermediate and proximal). In this model, the socioeconomic determinants of the mother, family, household and neighborhood play indirect effects on PB through variables at the intermediate level, which in turn affect biological risk factors at the proximal level that have a direct effect on PB. The study presents a hierarchical theoretical model of the factors involved in the PB determination chain and their interrelationships. Understanding these interrelationships is an important step in trying to break the causal chain that makes some women vulnerable to preterm birth.

Key words Preterm birth, Risk factors, Theoretical models

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Introduction

Preterm birth (PB) is defined as every birth which takes place before 37 full weeks of pregnancy, or in less than 259 days since the first day of the last menstrual period (LMP)1. Global estimates show an increase in the preterm birth rate over the years, varying between 9.8% in 2000 and 10.6% in 2014. This increase is equivalent to an estimated number of 14.6 million preterm births around the world². In 2016, the complications of PB were considered the main cause of death among children under the age of five, corresponding to approximately 16% of all deaths, and 35% of deaths among newborns3. In addition to its contribution to mortality, PB has effects throughout the lives of the survivors, with consequences related to neurological and cognitive deficits, visual/auditory deficiency, and an increased risk of chronic diseases in their adult lives^{4,5}.

PB can be subdivided into categories, based on the newborn's gestational age: extremely (< 28 weeks); very (\geq 28 and < 32 weeks), and moderate-to-late preterm (≥ 32 and < 37 complete weeks of pregnancy)6. These subdivisions are important, since the reduction in gestational age is associated with the newborn's survival and neonatal complications⁷. PB may also be classified into two large subtypes: (i) spontaneous preterm birth, defined as the spontaneous start of labour, or following the premature rupture of membranes (PRM); and (ii) premature labour started by health professionals (previously called "iatrogenic"), defined as induction of labour, or elective caesarean, before 37 full weeks of pregnancy, due to maternal or fetal indications, or other non-medical reasons8.

PB is a syndrome which results from a complex relationship between sociodemographic, psychosocial, nutritional, behavioural and biological maternal factors. However, although these risk factors are well-known in literature, the cause and relationship between them are not fully understood9. Therefore, theoretical models have been proposed, in the attempt to explain potential interrelationships between the various risk factors when determining results in health^{10,11}. However, the use of a hierarchical theoretical model to construct reviews on the determinants of PB is a differential and innovative approach. Thus, this article involving the review of literature, presents a hierarchical theoretical model of the determinants of preterm birth, providing subsidies to further discussion on the interrelationship of these different determinants.

Determinants of preterm birth

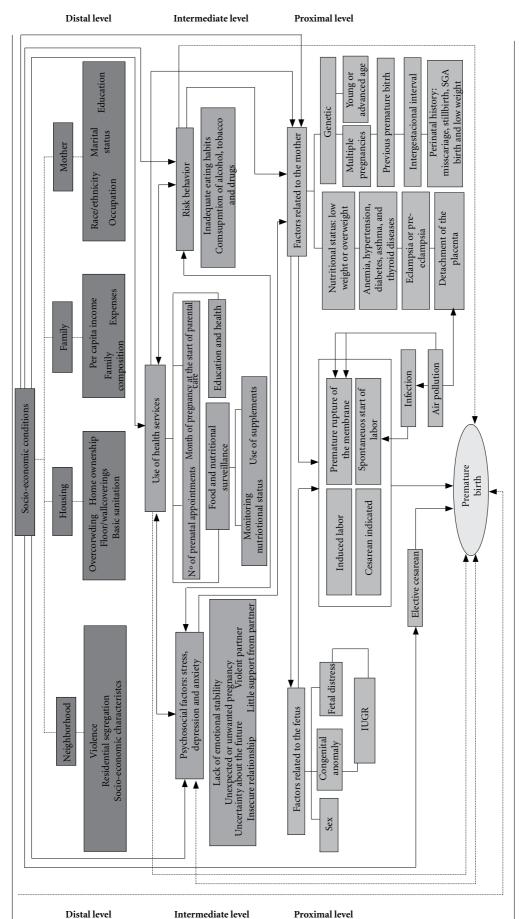
The complexity of a health outcome may be observed both through the influence that each of the factors exerts on its occurrence, and the interrelationships and interdependences of these different factors¹². A preterm birth prediction at a closer level can be determined by biological factors, such as a previous preterm labour, multiple pregnancy, maternal comorbidities, such as hypertension and diabetes, and other conditions related to the newborn, such as intrauterine growth restriction (IUGR) and fetal distress^{5,13}. Factors which represent the mother's lifestyle, psychological health, and healthcare, may possibly be observed at the intermediate levels of determination. Lastly, in general, the more distal factors refer to the mother's socio-economic and demographic conditions.

Based on an extensive review of literature, a hierarchical theoretical model of the determinants of preterm birth was proposed, which describes the interrelations between the variables that form each level of its determination (Figure 1). In the model presented, the variables were distributed into six dimensions, within three hierarchical levels (distal, intermediate, and proximal). The variables of a same dimension are connected by continuous lines. The direct effects between the different levels of determination, or different dimensions at the same level, are represented by arrows. The double arrows indicate the dimensions which establish bidirectional relationships between themselves. The indirect effects between the dimensions of different levels on the outcome are represented by dashed arrows. Lastly, the direct effects on the outcome, exercised by determinants located at the proximal level, are represented by arrows.

Distal determinants

Socio-economic determinants have been consistently identified as distal risk factors associated with preterm birth. Socio-economic status (SES) is an important predictor of health disparities, since socio-economically underprivileged groups tend to have worse health outcomes¹⁴. The economic dimension, represented in particular by family income, education and occupation, plays an important role in the determination, and adverse results of pregnancy¹⁵.

Income is highlighted as one of the most important socio-economic factors related to social inequality and, consequently, health inequali-



 $\textbf{Figure 1.} \ \textbf{Hierarchical theoretical model of the determinants of preterm birth. } \\$

IGR: intrauterine growth restriction; SGA: small for gestational age.

Source: Authors.

ties16. Differences in income determine the nature of people's working and housing conditions, access to food, and health services, which are explanatory factors on the paths in which income is associated with preterm birth¹⁷. Family income is equally important as individual socio-economic factors, to explain the relation between SES and health. Family income represents a standard of living, and life opportunities which family members experience by sharing goods and services¹⁸.

The educational level is a SES proxy which predicts health conditions with more strength and consistency, particularly for women and their children¹⁵. Women with a higher level of education have greater access to better jobs and income which, in turn, leads to access to essential goods, such as higher quality food. The level of education is also an important marker of access to health services, above all in relation to aspects such as the decision on the number and timing of the pregnancy, increased access and use of medical information, as well as the reduction of risk behaviour, such as the use of alcohol and tobacco19.

The impact of socio-economic inequalities also determines the nature of people's working conditions. The strenuous work carried out by women at a lower socio-economic level, often with a less education, is also associated with adverse birth results, including preterm birth20. Occupations characterised as heavy manual labour, under stressful conditions, with exposure to chemical agents, or a long period of time in the workplace, are factors which justify this relation^{21,22}.

In addition to income-related aspects, studies suggest an association between the maternal marital situation and results of the pregnancy^{23,24}. Single mothers suffer more from increased maternal stress related to uncertainty about the future, insecurity in the relationship, less emotional/social support, and economic disadvantage, when compared to mothers with partners^{23,25}.

The role of race/ethnicity in preterm birth has been reported in many studies which demonstrate variations in the length of the pregnancy among various ethnic groups^{26,27}. For black women, exposure to stressful psychosocial factors (poverty, lack of housing, living in dangerous neighbourhoods, domestic violence, and experience of discrimination, or racism), and risk behaviours associated with stress may favour the increased risk of preterm birth²⁸.

Residential segregation, defined as the extension to which social groups characterised by income or race/ethnicity are spatially separated from each other, may also contribute to preterm birth disparities²⁹. Residential segregation is a display of structural racism which affects opportunities in many dimensions, including economic well-being, education, and health³⁰. Women who reside in racially-isolated neighbourhoods accumulate disadvantages, such as less access to quality basic education, and higher economic and residential instability, which limits the opportunities associated with health improvements and increases stress, which may lead to negative birth outcomes³¹.

Housing is another social determinant associated with birth outcomes^{32,33}. Inadequate housing conditions (floor and wall coverings, exposure to mould, or humidity and basic sanitation) and household crowding are associated with a greater risk to health, mainly for the occurrence of infectious and respiratory diseases, which constitute important risk factors for preterm birth^{32,34}. Household crowding is also a marker of poverty and social deprivation³⁵, which may be associated with preterm birth, considering that the number of people in a family may influence access to food and other essential services. Crowding may also trigger stress factors in the pregnant woman's health and well-being, exposure to risk factors associated with injuries in the home, social tension, and exposure to passive smoking³⁶. In addition, home ownership may attribute feelings of security and/or prestige to the individual, especially when compared to situations of instability such as rent (social or private) and makeshift homes, which are susceptible to eviction. This instability directly affects psychosocial commitment, which produces impacts during the pregnancy³³.

The socio-economic characteristics at the neighbourhood level are considered important determinants for adverse birth outcomes^{17,29}, independent of socio-economic measures at the individual level¹⁷. Characteristics of the area of residence may influence preterm birth through difference in access to health care and other essential goods, maternal psychosocial stress, and health behaviours¹⁷.

Studies suggest that violence in the neighbourhood of residence may also lead to an indirect effect on increased risk of preterm birth and other birth outcomes^{37,38}. Exposure to contextual violence may lead to fear and psychological stress, mainly in the first trimester of pregnancy, which could lead to prematurity. In addition, violence may also lead to additional indirect effects on results of the delivery, such as interrupted access to

health services, particularly prenatal services, and risk behaviours such as an increase in smoking and the consumption of alcohol during pregnancy, in response to stress³⁷.

Intermediate determinants

At the intermediate level of determination, maternal psychological health, risk behaviours and access and use of health services are associated with premature delivery⁵.

High levels of maternal stress, anxiety and depression during pregnancy may have a negative impact on the development of the fetus, and be associated with premature labour³⁹. The vulnerability of pregnant women to stress, anxiety, and depression may be increased by factors such as a lack of emotional stability, uncertainty about the future, unstable housing, insecurity in a relationship, little support from a partner, a violent partner, financial difficulties, an unplanned or unwanted pregnancy, and lack of an adequate social support system^{40,41}. In certain circumstances, pregnancy in itself may become a stressful and difficult life experience²³. These maternal psychosocial factors can be significant determinants of birth outcomes, acting through behavioural or physiological channels⁴².

In addition, women exposed to anxiety and stressful conditions during pregnancy have increased serum concentrations of the corticotropin-releasing hormone (CRH) and pro-inflammatory cytokines. These findings suggest systemic inflammation as a pathophysiological path through which anxiety and stress could increase the risk of preterm delivery^{43,44}. Maternal depression during pregnancy may be the result of disruption of the hypothalamic-pituitary-adrenocortical axis, which encourages the release of cortisol and catecholamines. These biological alterations may result in placental hypoperfusion, and the consequent restriction of oxygen and nutrients to the fetus, which leads to restricted fetal growth and/or precipitating a preterm birth^{45,46}. Prenatal depression may be another factor which affects the functioning of the immunological system which, in turn, may lead to infection of the reproductive tract and preterm birth⁴⁵. An increase in smoking, the use of drugs and alcohol, poor diet, and less frequent use of the health service among women with depression may also contribute to worse maternal psychological health39.

Although the biological effects of the majority of chemical products present in smoking

cigarettes are unknown⁴⁷, it is known that nicotine and carbon monoxide are potent vasoconstrictors associated with placental damage, and a decrease in uteroplacental blood flow. This may lead to restricted fetal growth, which is one of the risk factors for preterm birth^{9,48}. Smoking is also associated with a systemic inflammatory response, which may increase spontaneous preterm birth in this way^{49,50}.

High alcohol consumption is also a behavioural factor associated with the risk of preterm birth51,52, which may be related to an increase in the secretion of prostaglandins and uterine contractions^{52,53}. In addition, alcohol may increase the risk of hypertensive disorders during pregnancy, which is one of the risk factors for preterm birth⁵⁴. The use of chemical substances and heroin have also been associated with adverse results of pregnancy, due to recurrent intrauterine hypoxic stress⁵⁵. Maternal exposure to narcotics may induce fluctuating cycles of intoxication and abstinence to the fetus, which may not have its oxygen needs met during abstinence⁵⁶. Simultaneously, other health problems associated with high risk behaviour among users of these substances, including insufficient prenatal appointments, restricted food intake, and an increase in maternal infections, may also increase the risk of preterm birth^{57,58}.

Maternal diet and eating habits may also favour a preterm birth^{59,60}. The experience of food insecurity, when there is no guarantee of regular and permanent access to quality food and in sufficient quantities⁶¹, is a prevalent condition among women with a low-income¹⁷. In addition, food insecurity precedes stages of nutritional shortcomings which may have a negative effect on fetal growth and birth results⁶².

Similarly, access and use of health services are associated with preterm birth⁶³. Studies indicate that the number of prenatal appointments, late start of prenatal appointments, and prenatal quality, have a strong influence on the occurrence, or otherwise, of a preterm birth^{64,65}. Despite the expansion of prenatal assistance coverage in Brazil in recent decades, regional and social inequalities in access to adequate prenatal assistance remain⁶⁶. Therefore, women with a lower probability of having access, and regularly attending prenatal appointments during pregnancy, are more prone to attaining adverse results during pregnancy or delivery⁶³. In addition, prenatal assistance may also be considered a mediator of maternal socio-economic conditions⁶⁷.

Proximal determinants

Among the proximal determinants of preterm birth, maternal factors, and those associated with the fetus can be highlighted^{5,9}. Young and advanced maternal ages have been associated with an increased risk of prematurity9. The high risk of a preterm birth in adolescence occurs due to biological immaturity, blood supply of the uterus or cervix⁶⁸, and competition for nutrients between the fetus and pregnant adolescent⁶⁹. This association may also be related to the psychological and socio-economic consequences that a teenage pregnancy may cause⁶⁸. At advanced ages, in other words, mothers aged ≥ 35 at the time of birth, a preterm birth may be associated with pre-existing maternal conditions, such as high blood pressure, and other obstetric complications⁷⁰ which are more frequent in this age group.

Maternal nutritional status during pregnancy, specifically low weight or pre-gestational obesity, may increase the risk of preterm birth through different potential mechanisms^{71,72}. For malnourished women, a preterm birth may be related to vulnerability to infection, associated with low concentrations of vitamins and minerals, which leads to a decrease in blood flow^{73,74}. On the other hand, excess maternal weight may also be related to a higher risk of complications during pregnancy, responsible for a medically-induced preterm birth, such as pre-eclampsia and diabetes9,75.

A short interval between pregnancies (for example, less than 18 months) has also frequently been associated with an increased risk of preterm birth^{9,76}. Short intervals between pregnancies increases the risk of a preterm birth, due to the time that the uterus takes to return to its normal state, including resolution of the inflammatory status associated with a previous pregnancy^{9,77}. A further association is related to maternal nutritional and folate depletion, since maternal stocks of essential vitamins, minerals, and amino-acids may be scarce in a short interval between pregnancies^{9,77}. It is important to highlight that in low- and middle-income countries, a mother's socio-economic status, lower level of education, and younger age, are frequently associated with short intervals between births⁷⁸. Similarly, long intervals (for example, more than 60 months) between pregnancies are associated with an increased risk of preterm birth77. It is possible that, physiologically, the mother returns to the physical state of a woman who has not yet been pregnant, which makes her less physically prepared for becoming pregnant⁷⁸.

Multiple pregnancies also represent a substantial risk of a preterm birth^{5,9}, since uterine hyperdistention may cause contractions and premature rupture of the membrane (PRM), this being a mechanism which triggers an increased rate of spontaneous preterm births⁷⁹. Additionally, the occurrence of pre-eclampsia, or other maternal or fetal disorders, may result in the preterm births indicated9. The growing availability of assisted reproduction in high-income countries has been put forward as a contributing factor for the high incidence of multiple births⁸⁰.

Infection is a frequent condition during pregnancy, which plays an important role in prematurity^{5,9,81}. The mechanisms through which intrauterine infections lead to premature labour are related to activation of the immune system and myometrial contractility, which may induce rupture of the membrane81,82 Among these, we highlight intrauterine, genital tract, and systemic infections81,82. However, it is not clear if infection is a cause, or consequence, of PRM. Intrauterine infection is recognised as one of the most important, and potentially avoidable, causes of preterm birth82.

Chronic maternal diseases, such as diabetes, hypertension, anaemia, asthma and thyroid disease, are associated with the increase in premature birth rates which, in many cases, are indicated due to maternal complications^{5,9}. Bidirectional relationships between preterm birth, low birth weight, and chronic non-communicable diseases (CNCDs), such as diabetes and hypertension, result in a vicious cycle of intergenerational risk⁸³. Women with CNCDs have a high risk of having a premature child. In turn, premature babies run a greater risk of developing CNCDs in adult life and, if they are female, of having a premature baby^{83,84}. Thus, women with chronic conditions during pregnancy require greater health and maternal care, including prenatal diagnosis and managing their CNCDs73.

A history of premature birth is also a risk factor for a subsequent preterm birth¹³. However, although preterm birth tends to be repeated, the mechanism for its recurrence is not always clear. It is believed that persistent or recurrent intrauterine infections probably account for many spontaneous, repetitive preterm births, and the continuity of underlying disorders for pregnancies which cause preterm births, such as diabetes, hypertension, or obesity9. Similarly, the risk factors shared by pregnancies (smoking during pregnancy, for example) may also contribute to the recurrence of premature birth^{85,86}.

Other adverse events in a previous pregnancy have also been described in literature, such as the risk of a preterm birth in a subsequent pregnancy, for example miscarriage, stillbirth, small baby for the gestational age, placental abruption, and pre-eclampsia^{87,88}. Weakening of the cervix, due to damage resulting from the surgical handling of a miscarriage, is a possible condition for these associations⁸⁹, as well as other common or shared conditions among the outcomes, such as abnormality in the placenta, with reduced placental perfusion^{90,91}.

Data in literature also demonstrates a genetic or epigenetic predisposition for preterm birth^{92,93}. Some of the evidence of genetic contribution in preterm birth is genetic heritability shown in studies conducted with twins; increased risk of the recurrence of premature birth in women with a previous prematurity; women who were born premature presenting an increased risk of having a premature birth; increased risk of premature birth among sisters and daughters of women who had a premature birth; and racial disparities in preterm birth which are independent of socio-economic factors82. Studies with candidate genes identified more than 30 single nucleotide polymorphisms (SNPs) predominant in inflammatory pathways and tissue remodelling, associated with increased or decreased risks of preterm birth, or PRM94.

In addition to maternal factors, risk factors related to the fetus are also associated with preterm birth⁵. A pregnancy with a male fetus has been associated with an increased risk of complications in pregnancy and adverse obstetric outcomes, for example, due to a higher incidence of premature labour for this sex⁹⁵. Possible mechanisms have been proposed to explain this association, such as the relatively higher weight of male, compared to female fetuses, and greater susceptibility to complications in pregnancy (hypertension or infection) in women carrying a male fetus⁹⁶.

A preterm birth started by health professionals or, in other words, induced labour or elective caesarean, is associated with maternal and fetal indications, or other non-medical reasons⁸. The most important direct causes, recognised as maternal and fetal complications, are pre-eclampsia, placental abruption, intrauterine growth restriction (IUGR), and fetal distress. However, these conditions may also predispose the spontaneous start of labour in premature gestational ages⁹⁷.

Pre-eclampsia is the most serious form of hypertensive disorder in pregnancy, and is associated with the preterm birth indicated 98,99. Higher blood pressure levels are associated with IUGR and, consequently, preterm birth 99. Obstetric intervention before term may also explain the association between pre-eclampsia and premature birth, considering that when blood pressure becomes uncontrollable and/or eclampsia occurs, an early intervention to empty the uterus becomes the option to deal with women with hypertensive complications in pregnancy 98.

Placental abruption is characterised by chronic placental dysfunction and separation from the uterine wall, the progression of which may lead to a corresponding reduction in the placental surface area available to exchange oxygen and supply nutrients to the fetus¹⁰⁰. In addition, placental abruption may progress to a significant loss of maternal blood, hypoxia and fetal death, as well as requiring an emergency cesarean^{101,102}. These processes may increase the risk of preterm birth.

IUGR is a common complication of pregnancy, and is associated with fetal (congenital anomalies and infections), placental insufficiency, or maternal factors (poor nutrition, smoking, and gestational hypertension)^{103,104}. Restricted blood flow to the fetus is a common element in the majority of pregnancies with IUGR, which results in a lack of oxygen and supply of nutrients to the fetus¹⁰³.

Fetal distress is the term used to describe fetal asphyxia or, in other words, a fetus with compromised gas exchange during the pre-labour or intrapartum phase. Fetal hypoxia resulting from this compromise, if it is not reversed, or delivery is unnecessarily delayed, may lead to permanent damage, or death of the fetus¹⁰⁵. Fetal distress requires immediate intervention, being in the urgent category for a caesarean and, consequently, premature birth started by health professionals¹⁰⁶.

The rise in prematurity rates worldwide is frequently associated with the increase in obstetric interventions, such as induced labour and caesarean delivery107. Caesarean rates have risen in recent decades¹⁰⁸, with the majority boosted by an increase in the use of caesareans without medical indication¹⁰⁹. A number of authors highlight that elective caesareans are more frequent among women who receive private health care during delivery, with higher levels of education, and a more favourable economic situation¹¹⁰. In addition, changes in maternal characteristics and professional practice, as well as economic, organisational, social and cultural factors, have been described as some of the factors related to the rise in preterm birth rates¹¹¹.

In addition, newborns with congenital anomalies, including neural tube defects, are more prone to premature births⁵. The mechanism for this association has not been fully clarified, considering that premature birth and congenital malformations are conditions which have common risk factors112. The prenatal diagnosis of a fetal malformation may also lead to induced labour or a caesarean delivery, independent of gestational age¹¹³.

Lastly, environmental exposure has also been associated with adverse results of pregnancy in different studies114-116. Air pollution [particulate matter; ozone (O3); sulphur dioxide (SO2); nitrogen dioxide (NO2); airborne particles (PM25 and PM₁₀); carbon monoxide (CO) and lead] may be directly associated with preterm birth through different biological mechanisms¹¹⁴⁻¹¹⁶. PM_{2.5} may induce rupture of the membrane and placental abruption,117 and increase intrauterine inflammation¹¹⁸. Similarly, ozone exposure may cause the release of proinflammatory mediators, which contribute to preterm birth¹¹⁹.

Final considerations

Preterm birth is a complex, multifactorial phenomenon involving a network of causal mechanisms which cannot all be covered in a single model, as proposed in this review. However, the use of a hierarchical model in an analysis of the determinant factors of preterm birth is a possible and always applicable approach, anchored in a review of pertinent literature on the topic. Combined with this, considering the complexity of preterm birth, it is only one of the possible hierarchical approaches, and new models could be proposed in this segment.

In the model presented, the factors in the distinct levels of determination interrelate, influencing the occurrence of preterm birth. The socio-economic determinants were classified as distal risk factors which indirectly act on preterm birth through intermediate variables, for example, healthcare, psychosocial and behavioural factors, which are expressed in food, tobacco and alcohol consumption patterns, among others. These variables may be influenced by the mother's socio-economic condition, family, housing, and neighbourhood. These intermediate factors determine the proximal level, which are those related to the mother, pregnancy, delivery, and fetus. At the proximal level, biological risk factors have a direct effect on preterm birth, with these being influenced by factors situated at higher (distal variables) and lower levels (intermediate variables).

We hope that this model can serve as a theoretical base for statistical modelling in studies that evaluate the interrelationships and effects of mediating the determinants of preterm birth. The proposal is to test this in a large cohort of births. We hope that the application of this hierarchical model may contribute to understanding the risk factors of preterm birth and its interrelationships. In addition, that it may contribute towards the development of specific strategies to prevent preterm births, in an attempt to interrupt the chain of determination of this outcome.

Collaborations

All of the authors contributed significantly to the investigation, read, and agreed with the final version of this manuscript.

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