REVIEW ARTICLE

Pregnancy: A window of opportunity for refining and mitigating the fetal origins of adult health and disease, and maternal cardiovascular futures

Hermanto Tri Joewono*
Master Program in Medical Education, Universitas Airlangga Teaching Hospital, RSIA(MCH) IBI Surabaya, Indonesia.

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***Corresponding author:**
Hermanto Tri Joewono
hermanto.tri@fk.unair.ac.id

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SUMMARY

This review explores the profound impact of pregnancy on fetal development and long-term maternal cardiovascular health, emphasizing how early-life conditions shape lifelong health. The concept of Fetal Origins of Adult Disease (FOAD) or Developmental Origins of Health and Disease (DOHaD) is discussed, highlighting how maternal nutrition and environmental factors during pregnancy predispose offspring to chronic diseases later in life. Maternal mental health is also explored, with depression and anxiety during pregnancy linked to lasting effects on offspring, including increased risks of mental health disorders and chronic conditions in adulthood. The study "Like Mother, Like Daughter" is examined to illustrate intergenerational risks such as preeclampsia and intrauterine growth restriction (IUGR), emphasizing the role of maternal health. Additionally, the long-term cardiovascular consequences of adverse pregnancy outcomes—such as preeclampsia, gestational diabetes, and preterm birth—are discussed, noting that they elevate the mother's risk of cardiovascular disease (CVD) in later life. The rising prevalence of obesity during pregnancy further exacerbates these risks. The paper calls for a shift in obstetrics from a narrow focus on pregnancy management to a broader approach that addresses both maternal and fetal health for long-term benefits. By recognizing pregnancy as a critical window to influence future health, comprehensive strategies could help mitigate chronic diseases in both mothers and children.

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Highlights:

1. Maternal nutrition, mental health, and environmental factors during pregnancy significantly influence the long-term physical and mental health of offspring, supporting the concept of Fetal Origins of Adult Disease (FOAD) and Developmental Origins of Health and Disease (DOHaD).
2. Adverse pregnancy outcomes like preeclampsia and gestational diabetes increase the mother's future risk of cardiovascular disease, highlighting the need for broader maternal health strategies beyond childbirth.

INTRODUCTION

Pregnancy is a critical period that offers a unique window of opportunity to shape the future health of both the child and the mother. This review begins with the understanding that human brain growth and development commence in the womb, making the prenatal environment crucial for optimal neurological outcomes.[1-4] It then proceeds to explore the concept that early-life conditions can set the stage for lifelong health outcomes,[5-9] as evidenced by unintended historical events such as the Dutch Hunger Winter.[10-11]

The influence of maternal mental health on fetal development is also a key area of concern.[12] The study by Sherf et al., "Like Mother, Like Daughter," exemplifies how maternal conditions such as preeclampsia and intrauterine growth restriction (IUGR) can transmit health risks across generations, further highlighting the intergenerational impact of maternal health.[13]

Adverse pregnancy outcomes, such as preeclampsia, gestational diabetes, preterm birth, and IUGR, are now recognized as significant risk factors for the development of cardiovascular disease (CVD) in mothers. The rising prevalence of obesity during pregnancy exacerbates the future risk of CVD for mothers, underscoring the need for comprehensive strategies to address maternal health.[14-30]

This review explores the profound impact of pregnancy on both fetal development and maternal cardiovascular health, advocating for a broader understanding of pregnancy as a crucial period for long-term health intervention. By expanding the focus beyond the traditional approach that narrowly addresses pregnancy, birth, and the puerperium, this paper aims to highlight the importance of addressing the broader and long-term implications of maternal and fetal health. Such an approach holds significant potential to mitigate the risk of chronic diseases in both the child and the mother, leading to healthier futures for both

OVERVIEW

Human brain growth and development – the forgotten amazing growth and development

Research, particularly by Stiles and Jernigan, has highlighted the critical importance of brain growth and development that begins in the womb, encompassing key processes such as neurulation, proliferation, migration, differentiation, myelination, apoptosis, and synaptogenesis. These foundational events in brain development occur prenatally and may be more crucial than those occurring after birth. Notably, by around 26 weeks of pregnancy, neuronal proliferation ceases, meaning that humans are born with fewer neurons than they had in utero. This challenges earlier models, such as Shonkoff's brain growth chart, which emphasized postnatal growth and development. Prenatal brain development is also significantly influenced by environmental enrichment and genetic factors, setting the stage for lifelong cognitive and neurological function.

Interestingly, hearing is the first sense to develop fully while the fetus is still in the womb, underscoring the complexity and early onset of sensory development (Figure 1). This prenatal period is therefore not only crucial for establishing the basic architecture of the brain but also for determining how it will interact with and adapt to the environment after birth.[1-4] Studies on environment enrichment by Mozart compositions during pregnancy by Hermanto TJ et al in Surabaya on human and animal models, should be noted even though on small number of population.[30]

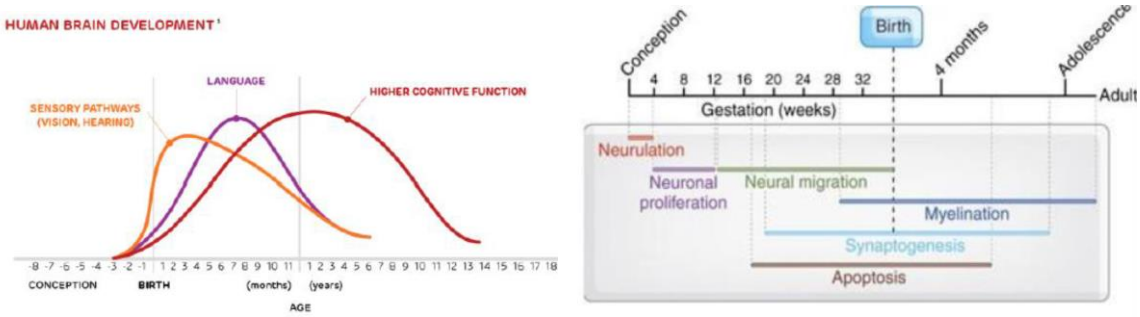

Figure 1. We have to change our perspective on human brain growth: the milestones are in the womb.[3,4]

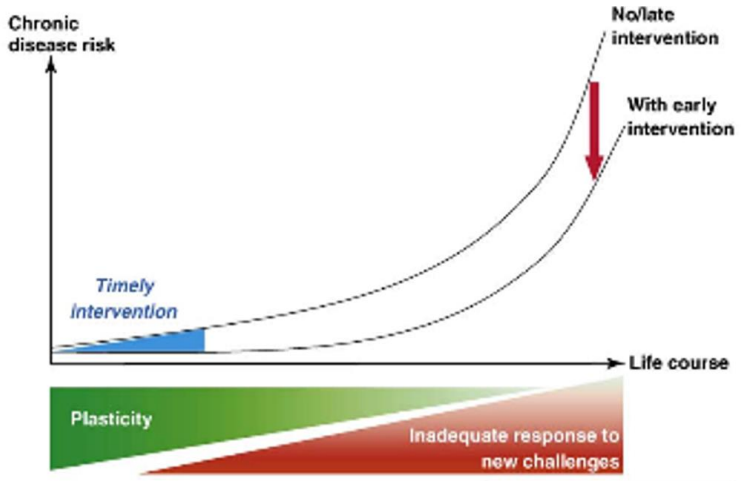

Figure 2. Relationship between early intervention vs impact,[7] but it does not explain the importance of the pregnancy period compared to the postnatal period

FOAD (fetal origins of adult disease) – important of life in the womb

The fetal origins of adult disease hypothesis, pioneered by David Barker, posits that the conditions experienced by a developing fetus can significantly influence long-term health outcomes. This groundbreaking theory emerged from Barker's observations in the 1980s, where he noted a correlation between low birth weight and higher rates of chronic diseases such as cardiovascular conditions and diabetes in adulthood. Barker suggested that environmental factors, particularly maternal nutrition during pregnancy, play a crucial role in shaping the fetal environment. Stress, inadequate nutrition, and other prenatal exposures can lead to adaptive changes in the developing fetus, which may predispose individuals to various health issues later in life. This paradigm shift not only emphasizes the importance of maternal health and prenatal care but also highlights the intricate connections between early life experiences and long-term physiological outcomes, underscoring a critical window during pregnancy that can have profound implications for public health and disease prevention strategies.[5]

DOHaD (developmental origins of health and disease) – not only in the womb or birthweight

The developmental origins of health and disease (DOHaD) hypothesis, articulated by Mark Hanson and Peter Gluckman, expands upon the ideas of fetal programming by emphasizing the intricate relationship between early life exposures and subsequent health outcomes throughout an individual's lifespan. This hypothesis posits that the environment experienced by a fetus—shaped by maternal nutrition, stress, and overall health—can lead to biological adaptations that, while beneficial for survival in the short term, may predispose individuals to chronic diseases such as obesity, diabetes, and cardiovascular issues later in life. Hanson and Gluckman argue that these adaptations are a response to the anticipated conditions of the external environment, meaning that a mismatch between early life conditions and later life realities can lead to adverse health effects. Their work underscores the importance of ensuring optimal maternal health and nutrition during pregnancy, as well as addressing social determinants of health, to improve outcomes not just for mothers and infants, but for future generations. By framing health as a continuum that begins in utero, the DOHaD hypothesis has significant implications for public health strategies, highlighting the need for early interventions that can mitigate risk factors and promote healthier lives (Figure 2).[6-9]

Dutch Hunger Winter – an unintended clinical trials study

The Dutch Hunger Winter of 1944-1945 serves as a poignant case study in the effects of maternal mal-nutrition during pregnancy, illuminating the profound impact that extreme environmental stressors can have on fetal development. During this harrowing period, a severe food blockade led to widespread famine in the Netherlands, with pregnant women facing acute shortages of essential nutrients. Research has shown that infants born during this time exhibited not only reduced birth weights but also increased susceptibility to a range of health issues later in life, including cardiovascular diseases, metabolic disorders, and mental health challenges.[10]

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The experiences of those affected by the Hunger Winter underscore the principles of the developmental origins of health and disease hypothesis, revealing how prenatal exposures to starvation can trigger lasting biological changes. For instance, studies tracking this cohort have demonstrated that individuals who were exposed to starvation in utero exhibited altered epigenetic patterns, which may influence gene expression related to growth and metabolism. This phenomenon illustrates the critical role that early life conditions play in shaping lifelong health trajectories, reinforcing the importance of maternal nutrition as a foundational aspect of public health.[11]

Furthermore, the legacy of the Dutch Hunger Winter extends beyond individual health outcomes, highlighting the broader societal implications of maternal well-being. The psychological and social impacts of famine on families and communities during this time serve as a reminder that maternal and child health cannot be isolated from the socio-political context. This historical event has spurred ongoing research into the long-term effects of prenatal adversity, advocating for policies that prioritize maternal nutrition and health as vital components of disease prevention strategies, ultimately fostering healthier future generations.[10-11]

Maternal mental health: Standing ovation for Alain Gregoire at Paris FIGO Congress 2023

Maternal mental health is a crucial aspect of prenatal care, as conditions such as depression during pregnancy can have profound implications not only for the mother but also for the developing child. Research indicates that maternal depression can disrupt the intricate bonding process between mother and child, potentially leading to attachment issues and emotional disturbances in the offspring. This disruption may manifest in various ways, including behavioral problems and cognitive delays, which can persist into adulthood. Of note, Alain Gregoire, a prominent expert in perinatal psychiatry, has consistently emphasized the critical importance of addressing women's mental health during pregnancy. He argues that the psychological well-being of expectant mothers is not only vital for their own health but also for the development and future well-being of their children. Gregoire highlights that pregnancy is a period of immense physical and emotional change, making women particularly vulnerable to mental health issues such as depression and anxiety. He advocates for comprehensive mental health support systems that are integrated into prenatal care, ensuring that women receive the necessary resources and interventions to manage stress, trauma, and other psychological challenges during this crucial time. By prioritizing mental health care during pregnancy, Gregoire believes that we can significantly improve outcomes for both mothers and their children, leading to healthier families and communities.[12,13]

The intergenerational transmission of mental health issues is a significant concern. Children of mothers who experience depression during pregnancy are at a higher risk of developing their own mental health disorders, such as anxiety and depression later in life. The underlying mechanisms may involve both genetic predispositions and environmental factors including the quality of the mother-child relationship and the home environment. For instance, a mother's depressive symptoms can affect her parenting style, leading to less responsive and nurturing interactions, which are essential for healthy emotional development. Furthermore, the stress experienced by mothers during pregnancy can alter fetal development. Elevated levels of stress hormones, such as cortisol, may affect brain development, potentially leading to long-term cognitive and emotional challenges for the child. Studies have shown that children exposed to high maternal stress during pregnancy are more likely to exhibit behavioral issues, mood disorders, and difficulties in social relationships as they grow older. Addressing maternal mental health is therefore critical not only for the well-being of the mother but also for breaking the cycle of mental health issues across generations. Early intervention and support for expectant mothers can significantly reduce the risk of developing long-term mental health problems in their children. Creating a strong support system, including mental health resources, social support, and prenatal education, can foster resilience and promote healthier outcomes for both mothers and their children. Understanding the link between maternal depression during pregnancy and long-term mental health outcomes in offspring highlights the need for comprehensive mental health care in prenatal settings. By prioritizing maternal mental health, we can create a positive ripple effect that enhances the well-being of families and mitigates the risk of mental health disorders across generations.[12-14]

Study of Sherf et al., "Like Mother, Like Daughter"

In the triad study "Like Mother, Like Daughter" by Sherf et al., the researchers explore the transgenerational implications of preeclampsia and intrauterine growth restriction (IUGR). The narrative begins with the recognition that maternal health conditions during pregnancy can have lasting effects, not only on the immediate offspring but also on subsequent generations. The study highlights how daughters of mothers who experienced preeclampsia are at a heightened risk of developing similar complications in their own

pregnancies, suggesting a hereditary component to these conditions. Sherf et al. delve into the biological mechanisms that may underpin this transgenerational transmission, examining genetic, epigenetic, and environmental factors that contribute to the susceptibility of future generations. The researchers emphasize the importance of understanding these dynamics, as they can inform preventative strategies and clinical interventions aimed at mitigating risks for women with a family history of preeclampsia and IUGR. The findings underscore the critical need for healthcare providers to consider family history when assessing risks during prenatal care. By recognizing patterns that span generations, practitioners can better tailor monitoring and treatment plans. This study not only sheds light on the complex interplay of maternal health and offspring outcomes but also calls for further research to unravel the intricate pathways linking maternal experiences to the health of future generations. Ultimately, Sherf et al. advocate for a more holistic approach to maternal-fetal medicine that takes into account the legacy of maternal health conditions.[15] The "Collab team" appears to have explained the mechanism in their 2022 paper.[16]

Adverse Pregnancy Outcomes (APO) vs Maternal Future CardioVascular Disease (MFCVD)

Pregnancy is a critical period that can significantly influence a woman's long-term health, particularly concerning cardiovascular disease (CVD). Emerging research has highlighted a concerning link between adverse pregnancy outcomes—such as preeclampsia, gestational diabetes, preterm birth, and obesity—and an increased risk of future cardiovascular complications.[17,18] Preeclampsia, characterized by high blood pressure and damage to other organ systems, is one of the most significant pregnancy complications. Studies indicate that women who experience pre-eclampsia face a heightened risk of developing hyper-tension and cardiovascular disease later in life. The underlying mechanisms may include persistent vascular damage and altered metabolic profiles that persist long after delivery.[19-25]

Gestational diabetes mellitus (GDM) is another pregnancy-related condition that has been associated with long-term health implications. Women with a history of GDM are at increased risk for type 2 diabetes, which is a well-known risk factor for cardiovascular disease. The metabolic disturbances caused by GDM can contribute to endothelial dysfunction, a precursor to cardiovascular issues, highlighting the importance of monitoring these women post-pregnancy.[26-30]

Preterm birth also raises alarms regarding maternal health. Research suggests that women who deliver preterm may experience an increased risk of cardiovascular events later in life. The stress of preterm delivery and potential complications may lead to lasting changes in the cardiovascular system, necessitating ongoing surveillance for heart health in this population.[31,32]

Lastly, obesity during pregnancy compounds these risks. Maternal obesity is linked to a higher incidence of the aforementioned adverse outcomes, creating a cyclical pattern that exacerbates long-term cardiovascular risk. Women who enter pregnancy with obesity are more likely to develop complications like preeclampsia and gestational diabetes, further increasing their future cardiovascular burden.[33,34]

Table 1. Most probable mechanisms

Items	Mechanisms
FOAD DOHaD	Fetal programming via epigenetic modifications at least involving • altered DNA Methylation and • changes in histone acetylation/methylation
Dutch Hunger Winter	• Epigenetic Reprogramming of Metabolism • Stress-Induced HPA Axis Dysregulation • Endothelial Dysfunction & Cardiovascular Risk • Mismatch Hypothesis & Metabolic Adaptation
APO vs MFCVD	Complex and multifactorial, involving endothelial dysfunction, chronic inflammation, metabolic disturbances, oxidative stress, epigenetic changes, and shared genetic and lifestyle factors.
Environment Enrichment	Prenatal exposure to Mozart's 14-sequence music may enhance neuroplasticity by increasing BDNF and synapsin, while reducing neuronal apoptosis, supporting optimal brain development and cognitive function in the offspring

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Environmental enrichment and fetal brain capacity

Environmental enrichment during pregnancy, such as exposure to stimulating environments and adequate nutrition, has been shown to enhance fetal brain development. Research suggests that maternal engagement in cognitive activities, physical exercise, and a balanced diet can foster neurodevelopment, potentially increasing cognitive capacities in offspring. This emphasizes the significant role of the prenatal environment in shaping brain health and cognitive outcomes, pointing to the importance of maternal lifestyle and environment during pregnancy. The interplay between pregnancy outcomes, maternal health, and fetal development represents a complex and critical area of research. Understanding these relationships is essential for developing interventions that can promote better health outcomes for both mothers and their children. Continued exploration of how prenatal experiences influence long-term health can inform public health strategies aimed at reducing the burden of chronic diseases that are linked to early life conditions. This discussion highlights the need for a holistic approach to prenatal care that not only addresses immediate pregnancy outcomes but also considers the broader, long-term implications for maternal and child health.[35-41]

Most probable mechanism

The most probable mechanism remains a subject of ongoing investigation, marked by its inherent ambiguity due to its recent discovery and the intricate interplay of multiple contributing factors (Table 1). Rather than a singular, linear pathway, emerging evidence suggests a network of interconnected mechanisms operating in parallel or sequentially, influenced by dynamic physiological, molecular, or environmental variables. This complexity challenges traditional reductionist models, requiring an integrative approach that synthesizes diverse perspectives and methodologies. As research progresses, refining our understanding of this mechanism will necessitate advanced analytical techniques and interdisciplinary collaboration to disentangle its layered intricacies.

Relationship with SDG 3's goal

This paper aligns closely with the 3rd Sustainable Development Goal (SDG) on Good Health and Well-being by advocating for a holistic approach to maternal and fetal health that extends beyond pregnancy. By emphasizing the long-term benefits of addressing maternal mental health, managing conditions like preeclampsia, gestational diabetes, and intrauterine growth restriction (IUGR), the paper highlights how proactive maternal care can lead to healthier outcomes for both mothers and their children (Figure 3). This approach not only improves immediate pregnancy outcomes but also reduces the future burden of chronic diseases such as cardiovascular disease (CVD) in mothers, supporting healthier lifespans. Additionally, by focusing on intergenerational health—how maternal health impacts the child's lifelong well-being—the paper underscores the importance of addressing both maternal and fetal health comprehensively. This contributes directly to SDG 3's goal of ensuring healthy lives and promoting well-being for all ages by fostering a healthcare system that is empathetic, informed, and preventive, thus breaking cycles of poor health across generations.[42]

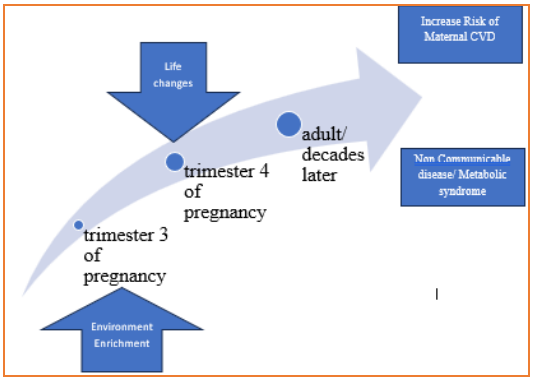

Figure 3. Proposed model for mitigating adult disease in the unborn child through environmental enrichment during third trimester of pregnancy, and reducing the increased maternal risk of future cerebrovascular disease through lifestyle changes during the fourth trimester — laying the groundwork for a healthier generation and ultimately transforming the landscape of public health for years to come.

CONCLUSION

In conclusion, the intricate interplay between maternal health during pregnancy and the long-term outcomes for both mother and child underscores the critical importance of this unique developmental window. As we have explored throughout this paper, pregnancy is not merely a period of gestation but a pivotal phase that holds the potential to shape lifelong health trajectories.

By refining our understanding of the fetal and developmental origins of adult health and disease, we can identify key interventions that may mitigate adverse outcomes. This knowledge empowers healthcare

providers to implement evidence-based strategies that promote maternal cardiovascular health and foster optimal fetal development.

Moreover, addressing maternal health proactively during pregnancy can lead to significant public health benefits, reducing the burden of chronic diseases that often emerge later in life. By recognizing and acting upon the vulnerabilities and opportunities present during this time, we can pave the way for healthier futures for both mothers and their children.

Ultimately, the narrative of pregnancy as a window of opportunity calls for a paradigm shift in how we approach maternal and child health. It emphasizes the need for a holistic view that integrates medical, social, and environmental factors, encouraging collaborative efforts among healthcare professionals, policymakers, and communities. As we move forward, let us commit to harnessing this critical period not only to improve maternal cardiovascular outcomes but also to lay the groundwork for a healthier generation, ultimately transforming the landscape of public health for years to come.

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