J. Perinat. Med. 2025; 53(4): 418–438 DE GRUYTER

Review

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Fetal origins of adult disease: transforming prenatal care by integrating Barker's Hypothesis with AI-driven 4D ultrasound

https://doi.org/10.1515/jpm-2024-0617
Received December 24, 2024; accepted February 21, 2025;
published online April 8, 2025

Abstract

Introduction: The fetal origins of adult disease, widely known as Barker's Hypothesis, suggest that adverse fetal environments significantly impact the risk of developing chronic diseases, such as diabetes and cardiovascular conditions, in adulthood. Recent advancements in 4D ultrasound (4D US) and artificial intelligence (AI) technologies offer a promising avenue for improving prenatal diagnostics and validating this hypothesis. These innovations provide detailed insights into fetal behavior and neurodevelopment, linking early developmental markers to long-term health outcomes.

Content: This study synthesizes contemporary developments in AI-enhanced 4D US, focusing on their roles in detecting fetal anomalies, assessing neurodevelopmental markers, and evaluating congenital heart defects. The integration of AI with 4D US allows for real-time, high-resolution visualization of fetal anatomy and behavior, surpassing the diagnostic precision of traditional methods. Despite these advancements, challenges such as algorithmic bias, data diversity, and real-world validation persist and require further exploration.

Summary: Findings demonstrate that AI-driven 4D US improves diagnostic sensitivity and accuracy, enabling earlier detection of fetal abnormalities and optimization of clinical workflows. By providing a more comprehensive understanding of fetal programming, these technologies substantiate the links between early-life conditions and adult health outcomes, as proposed by Barker's Hypothesis.

Outlook: The integration of AI and 4D US has the potential to revolutionize prenatal care, paving the way for personalized maternal-fetal healthcare. Future research should focus on addressing current limitations, including ethical concerns and accessibility challenges, to promote equitable implementation. Such advancements could significantly reduce the global burden of chronic diseases and foster healthier generations.

Keywords: Barker's Hypothesis; 4D ultrasound; artificial intelligence; prenatal diagnostics

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Introduction

The fetal origins of adult disease, commonly known as Barker's Hypothesis, propose that adverse conditions during fetal development can predispose individuals to chronic illnesses in adulthood, including cardiovascular disorders, diabetes, and metabolic syndromes [1, 2]. Central to this hypothesis is the concept of fetal programming, which underscores the significant influence of intrauterine environments on long-term health trajectories [3, 4]. By closely monitoring fetal growth patterns and behaviors, early markers of such conditions can be identified, enabling timely and targeted interventions [5, 6].

Recent advancements in prenatal diagnostic tools have revolutionized maternal-fetal care, with 4D ultrasound technology playing a pivotal role [2, 3]. Unlike 2D imaging, which captures static cross-sectional views, 4D ultrasound offers dynamic, real-time visualization of fetal anatomy and behavior [7, 8]. This enhanced capability facilitates a deeper understanding of neurodevelopmental processes and abnormalities, providing critical insights into the early indicators of adult health outcomes as outlined by Barker's Hypothesis [9, 10]. Despite these advancements, traditional diagnostic approaches still face challenges in detecting subtle abnormalities and establishing robust correlations with future health risks [11, 12].

The incorporation of artificial intelligence (AI) into prenatal care has further augmented diagnostic precision and predictive potential [13, 14]. When integrated with 4D ultrasound, AI algorithms can process intricate datasets, identify minor fetal anomalies, and streamline clinical workflows [15, 16]. Research has demonstrated AI's efficacy in advancing fetal cardiology, detecting congenital heart defects, and evaluating fetal behavior, thereby offering strong validation for Barker's Hypothesis [17, 18]. This intersection of AI and 4D ultrasound introduces a transformative paradigm for understanding and mitigating the impacts of fetal programming [19].

This study advances the field by leveraging AI-driven 4D ultrasound to explore how prenatal conditions shape long-term health risks through neurodevelopmental and physiological markers [20, 21]. The integration of AI enhances the ability of 4D ultrasound to identify fetal anomalies, placental dysfunction, and neurodevelopmental irregularities in real time, promoting earlier and more effective clinical interventions [22, 23]. By aligning the Developmental Origins of Health and Disease (DOHaD) framework with epigenetic science, this research illuminates the mechanisms through which environmental exposures during early development, such as DNA methylation and histone modifications, influence lifelong health outcomes [24, 25]. AI further amplifies this understanding by analyzing complex epigenetic patterns [26].

The study also addresses critical ethical and practical challenges in the implementation of AI-enhanced prenatal diagnostics, proposing strategies to mitigate algorithmic bias, diversify datasets, and expand access to scalable AI technologies in resource-limited settings [27, 28]. Moreover, it introduces a personalized maternal-fetal care model that combines predictive analytics, real-time imaging, and epigenetic insights to prioritize prevention and early interventions during the critical first 1,000 days of life [29, 30]. Finally, the use of AI-powered predictive models is demonstrated to effectively forecast complications such as preeclampsia and neurodevelopmental disorders, integrating maternal health data, fetal imaging, and epigenetic markers for timely and tailored clinical responses [31, 32].

The primary aim of this research is to explore the synergistic integration of AI and 4D ultrasound in validating Barker's Hypothesis by identifying early neurodevelopmental and physiological indicators predictive of adult diseases [33, 34]. Specifically, it seeks to address two core questions: (1) How can AI-enhanced 4D ultrasound improve the detection of fetal anomalies and neurodevelopmental patterns linked to long-term health risks? [35, 36] (2) What are the challenges and opportunities in integrating these advanced technologies into routine prenatal care to ensure equitable and effective implementation? [37, 38] By addressing these critical gaps in current diagnostic methods and harnessing state-of-the-art technology, this study contributes to the evolution of personalized prenatal care and the optimization of maternal-fetal health outcomes [39, 40].

Methods

This review adopts a scoping review framework to systematically synthesize the current literature on the integration of artificial intelligence (AI) and 4D ultrasound (4D US) technologies in prenatal diagnostics and their role in validating the Barker's Hypothesis. The scoping review methodology was chosen to comprehensively map the available evidence, identify research gaps, and explore the breadth of applications within this interdisciplinary field.

AI and 4D ultrasound workflow overview

The integration of AI with 4D ultrasound (4D US) involves a continuous, multi-stage process designed to optimize diagnostic precision and improve clinical decision-making. The workflow begins with data collection and preprocessing, where raw 4D ultrasound data from various fetal imaging studies are gathered and prepared. This stage ensures consistency by applying noise reduction techniques, normalizing image resolutions, and standardizing formats. Data augmentation methods, such as image flipping and rotation, are employed to increase the robustness of the AI models and prevent overfitting during training.

Once the data has been prepared, AI algorithms, particularly convolutional neural networks (CNNs), are utilized to extract essential features from the ultrasound images. Key features include fetal limb movements, facial expressions, heart rate variability, and markers of neurodevelopment. Specific submodules within the CNN architecture are designed to detect subtle indicators of fetal anomalies, such as abnormal motor patterns or irregularities in cardiac function. By focusing on these key indicators, the AI system can capture early warning signs of potential developmental or structural issues.

The development and training of the AI models play a central role in the workflow. The models are trained using labeled datasets containing fetal ultrasound recordings from diverse populations to minimize bias and enhance generalizability. Performance is measured using key metrics such as accuracy, sensitivity, and specificity to ensure reliable diagnostic outcomes. The models undergo further optimization through hyperparameter adjustments, improving their ability to detect anomalies with precision and consistency.

As the trained models analyze ongoing ultrasound scans, they provide real-time feedback and risk assessments. For example, if an anomaly is detected in fetal motor development, the AI system assigns a corresponding risk score, which is immediately presented to clinicians through an intuitive clinical interface. This real-time decision support enables healthcare providers to make timely and informed interventions, enhancing overall prenatal care.

Validation and testing constitute the final critical stage of the workflow. The AI models are rigorously validated using external datasets collected from multiple clinical centers, ensuring their performance across different populations and equipment configurations. Cross-validation techniques are employed to prevent overfitting and enhance the robustness of the models in real-world clinical settings.

Literature review process

A comprehensive search was conducted across multiple electronic databases, including PubMed, Scopus, and Web of Science, to identify relevant peer-reviewed studies. The search targeted publications from 2010 to 2024, reflecting recent advancements in AI-driven prenatal diagnostics. The search strategy employed combinations of key terms and Boolean operators to ensure broad coverage, including terms such as "Barker's Hypothesis", "Developmental Origins of Health and Disease (DOHaD)", "artificial intelligence", "4D ultrasound", "prenatal diagnostics" and "fetal programming". Filters were applied to limit the search to English-language studies. The search results were screened rigorously to select studies that met the eligibility criteria.

The inclusion criteria focused on studies that discussed AI or 4D US in prenatal care, specifically those addressing fetal programming in the context of DOHaD or Barker's Hypothesis. Eligible studies included original research articles, systematic reviews, and meta-analyses. Articles were excluded if they focused solely on 2D or 3D ultrasound without AI integration, lacked relevance to DOHaD principles or fetal programming, or were non-peer-reviewed publications such as commentaries or editorials. Studies that contributed meaningful evidence to the evaluation of early-life conditions and long-term health outcomes were prioritized.

The screening process was conducted in two phases to ensure thorough coverage and minimize bias. First, titles and abstracts of all retrieved articles were screened independently by two reviewers to exclude irrelevant studies. Following this, the full texts of the potentially relevant articles were reviewed in depth to determine their eligibility. Disagreements between reviewers were resolved through discussion or consultation with a third reviewer, ensuring a robust and transparent selection process.

Data extraction focused on collecting essential information from each included study, including study design, population characteristics, technologies used (AI and 4D ultrasound), key findings, and relevance to validating the Barker's Hypothesis. To ensure consistency, two reviewers independently extracted and verified the data. The extracted data were then systematically organized using tables to facilitate thematic analysis and synthesis.

Synthesis and analysis

The findings were synthesized using a narrative synthesis approach, allowing for the integration of diverse types of evidence. Key themes were identified, such as the diagnostic potential of AI-driven 4D US in detecting fetal neurodevelopmental and physiological markers, challenges related to clinical implementation, and gaps in current research. The synthesis highlighted how AI and 4D US contribute to early identification of developmental risks and the broader understanding of DOHaD principles.

Ethical considerations were observed throughout the review process by ensuring proper citation of sources and adherence to established publication ethics. As the review relied on secondary literature, ethical approval was not required. This comprehensive and structured methodology ensures transparency and reproducibility, providing a robust evaluation of the role of AI and 4D US in validating the Barker's Hypothesis and advancing prenatal care.

By incorporating a detailed description of the AI methodology, this study enhances its practical and technical clarity, making it accessible to both clinical and research audiences interested in leveraging AI-driven technologies for improved maternal-fetal outcomes.

Results and findings

Developmental Origins of Health and Disease (DOHaD): expanding Barker's Hypothesis

The Developmental Origins of Health and Disease (DOHaD) theory builds upon the Barker's Hypothesis by emphasizing how early-life environmental exposures influence lifelong health patterns through epigenetic modifications, such as DNA methylation and histone modifications [1, 5, 10]. As depicted in Figure 1, advances in molecular biology and artificial intelligence (AI) have revolutionized the ability to analyze large datasets, uncovering critical windows of developmental plasticity and identifying disruptions in key processes like neurogenesis and immune system programming [20, 41]. For example, maternal malnutrition disrupts pancreatic beta-cell development, increasing the risk of type 2 diabetes, while excessive glucocorticoid exposure recalibrates the stress-response system, heightening risks for neuropsychiatric disorders [14, 17] (Figure 2).

AI's integration into DOHaD research enables predictive modeling and personalized interventions aimed at mitigating lifelong disease risks stemming from early environmental exposures [42, 43]. The life-course perspective embedded within DOHaD highlights the mismatch hypothesis, which explains how early adaptive responses can become maladaptive under different postnatal conditions [5]. For instance, favorable postnatal environments may mitigate adverse prenatal effects, demonstrating the potential for resilience and recovery [2, 13]. Addressing disparities in maternal and child health aligns with DOHaD's broader focus on promoting disease prevention through social equity [44, 45].

Skeptics argue against deterministic interpretations, emphasizing that ongoing interactions between early and later exposures, including the microbiome's role in immune programming, can modify health outcomes [4, 11]. Animal studies provide robust evidence linking early environmental conditions to long-term health risks, while transgenerational epigenetic inheritance suggests that early exposures can affect not only immediate offspring but also subsequent generations [12]. These insights carry major public health implications, supporting the development of early-life interventions to reduce non-communicable diseases despite logistical challenges related to cost and feasibility (Figure 3) [16, 46] (Figure 4).

Fetal programming and the intrauterine environment: key drivers of adaptation

Fetal programming is a key concept explaining how environmental cues during gestation shape long-term health through adaptive developmental changes (Figures 5–9) [5, 6]. Mechanisms such as epigenetic regulation, metabolic adjustments, and neural plasticity allow the fetus to adapt to maternal signals but often result in long-term health tradeoffs [10, 12]. For example, maternal undernutrition prioritizes brain development over other organ systems, such as muscular or endocrine development, increasing the risk of metabolic disorders in adulthood [14, 17].

The placenta, serving as a mediator between the maternal and fetal systems, processes signals related to

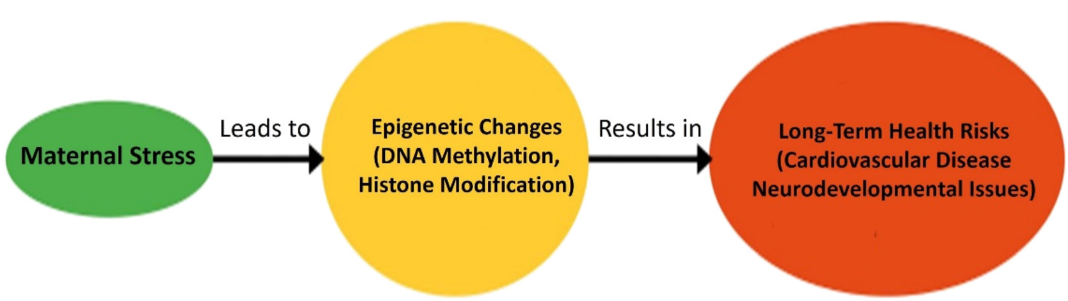

Figure 1: This illustration highlights the epigenetic processes central to Barker's Hypothesis, establishing a connection between prenatal maternal stress and enduring health implications. Stress experienced by mothers during gestation triggers epigenetic modifications – such as histone alterations and DNA methylation – that influence gene activity without altering the genetic code. These shifts in gene regulation increase the likelihood of chronic health conditions in offspring, including neurodevelopmental disorders and heart disease.

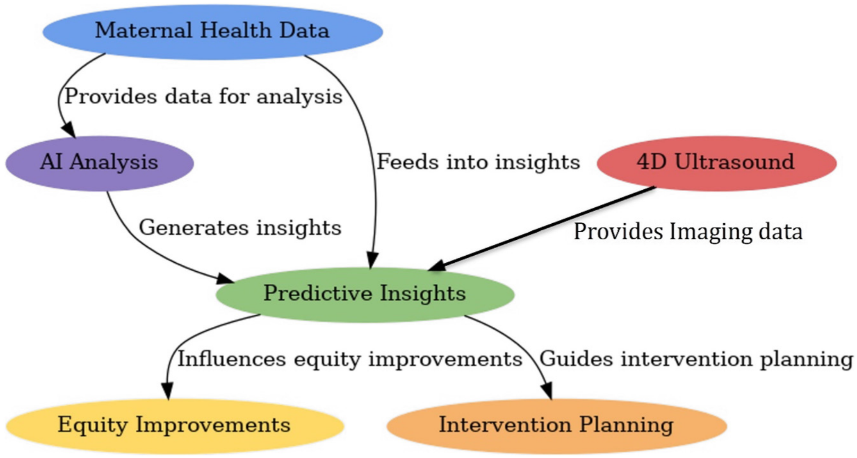

Figure 2: This graphic presents an AI-integrated approach to prenatal healthcare, grounded in the principles of Barker's Hypothesis. By utilizing maternal health metrics alongside advanced 4D ultrasound imaging, artificial intelligence generates forecasts regarding possible risks and health trajectories. These predictions support the development of targeted interventions, aiming to optimize maternal and fetal health while promoting equitable access to care.

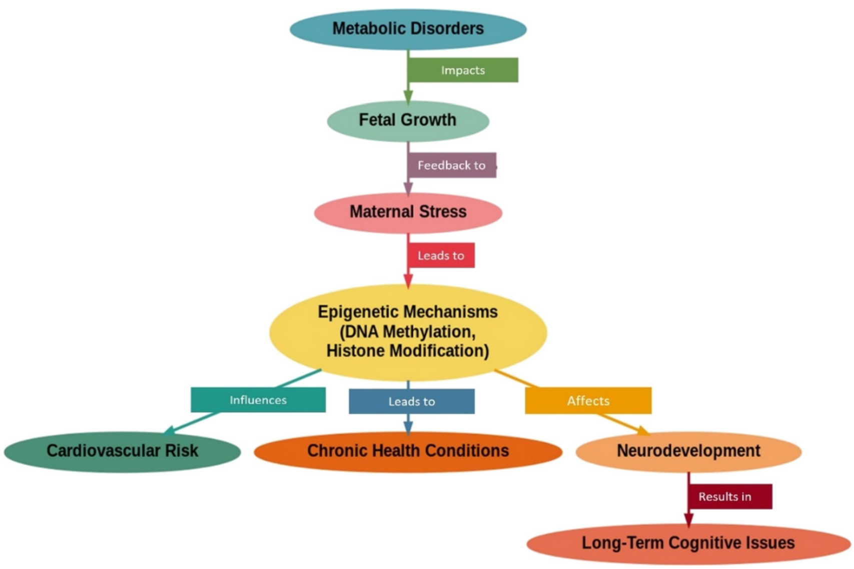

Figure 3: This visual representation outlines the interrelated mechanisms described by Barker's Hypothesis, focusing on the reciprocal effects of maternal and fetal health on lifelong outcomes. Maternal metabolic imbalances influence fetal development, creating a feedback loop that exacerbates maternal stress and activates epigenetic processes, such as DNA methylation and histone alterations. These changes in gene expression predispose offspring to enduring health challenges, including neurodevelopmental disorders, cardiovascular diseases, and cognitive decline.

nutrient availability, oxygen supply, and inflammatory markers (Figure 5) [30, 32]. This regulatory function determines resource allocation and influences growth trajectories. Impaired placental efficiency due to maternal stress or inadequate nutrition often results in redirected energy resources, predisposing offspring to conditions such as hypertension or insulin resistance [32, 47].

Elevated maternal glucocorticoid levels recalibrate the fetal hypothalamic-pituitary-adrenal (HPA) axis, increasing the likelihood of postnatal psychiatric disorders, such as anxiety and depression (Figure 6) [14, 18]. Environmental toxins, including endocrine disruptors, further exacerbate risks by interfering with hormonal feedback mechanisms, which can result in metabolic or reproductive disorders in adulthood (Table 2) [22]. Emerging evidence also highlights the role of maternal microbiota and infections in altering fetal immune programming, increasing susceptibility to inflammation and disease [4, 13].

Birth outcomes, such as low birth weight, serve as surface indicators of underlying fetal adaptations [16, 23]. As highlighted in Table 1, more nuanced assessments – including fetal heart rate variability and neurobehavioral activity – offer deeper insights into how intrauterine conditions shape developmental trajectories and influence long-term health [26, 39]. This understanding, coupled with evidence of transgenerational transmission of epigenetic marks, emphasizes the societal importance of improving maternal care and mitigating environmental stressors [12, 40] (Table 2).

AI applications in fetal programming and epigenetics

AI applications have enhanced the understanding of fetal programming and epigenetic mechanisms by analyzing

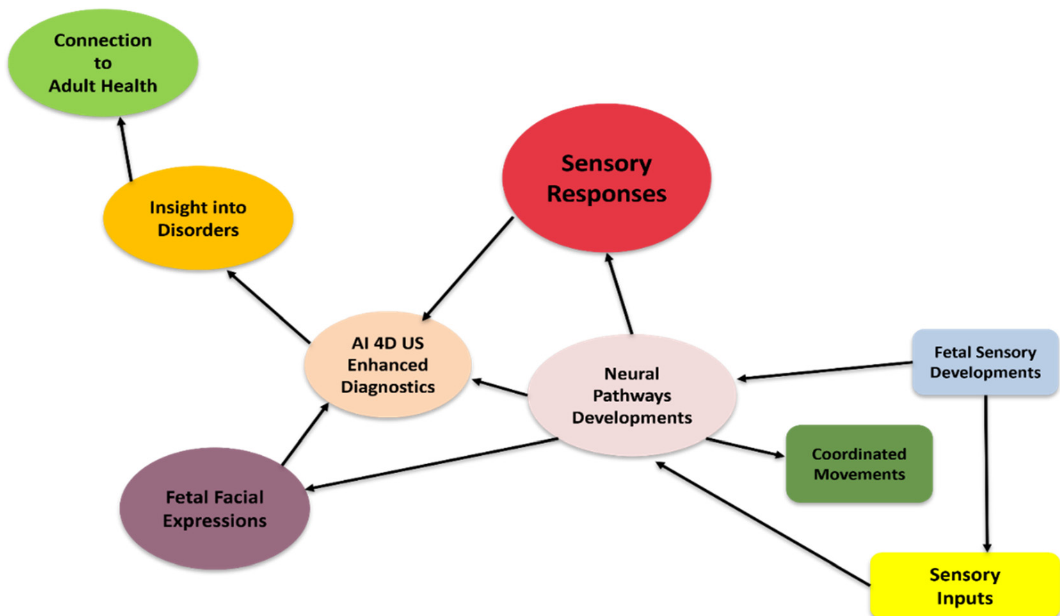

Figure 4: This diagram emphasizes the significance of sensory input and neural maturation in fetal programming as proposed by Barker's Hypothesis. Coordinated fetal movements and sensory stimuli foster the formation of neural pathways, influencing sensory processing and observable facial expressions. Advanced insights from AI-assisted 4D ultrasound technologies associate these developmental processes with potential long-term health risks, supporting early prediction and targeted interventions.

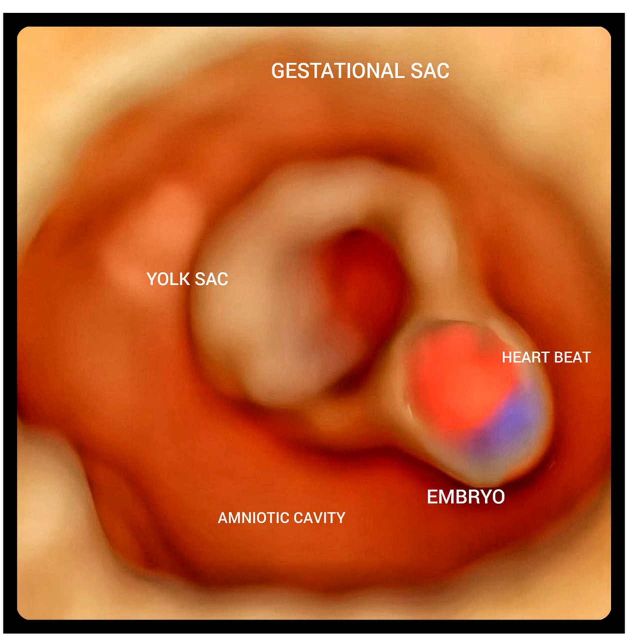

Figure 5: This 4D ultrasound captures the emergence of a detectable heartbeat between 5 and 6 weeks, illustrating the commencement of critical fetal physiological processes. Consistent with Barker's Hypothesis, this early cardiac activity highlights the pivotal role of maternal well-being and environmental influences during initial developmental stages. Stress or adverse conditions may instigate epigenetic alterations, such as DNA methylation, potentially affecting the growth of cardiovascular and neural systems. This observation underscores the importance of early maternal health monitoring and timely interventions to mitigate future risks of chronic illnesses and developmental challenges in adulthood.

complex biological data to identify developmental risks [42, 43]. Through AI-driven analysis of DNA methylation patterns and histone modifications, researchers gain valuable insights into how early environmental exposures shape long-term health outcomes, such as cardiovascular disease and diabetes [10, 24]. As demonstrated in Figure 12, integrating maternal health data, genetic information, and fetal imaging allows AI to deliver precise risk assessments and support early intervention planning, offering a proactive approach to safeguarding future health [20, 41].

AI-powered 4D ultrasound has proven effective in detecting neurodevelopmental anomalies by monitoring fetal movements, breathing patterns, and neurological markers, as illustrated in Figure 4 and Figure 11, which highlight key diagnostic applications [24, 31]. For instance, the Kurjak Antenatal Neurodevelopmental Test (KANET), supported by AI, evaluates fetal motor responses and brain development, offering clinicians an early window into potential developmental disorders [33, 39].

AI systems also enhance epigenetic research by linking environmental factors to specific molecular changes [10, 22]. For example, prenatal stress-induced DNA methylation of glucocorticoid receptor genes is associated with altered stress responses and anxiety disorders later in life [12]. The integration of AI in these analyses supports the identification of at-risk pregnancies and enables targeted interventions during critical developmental windows [48].

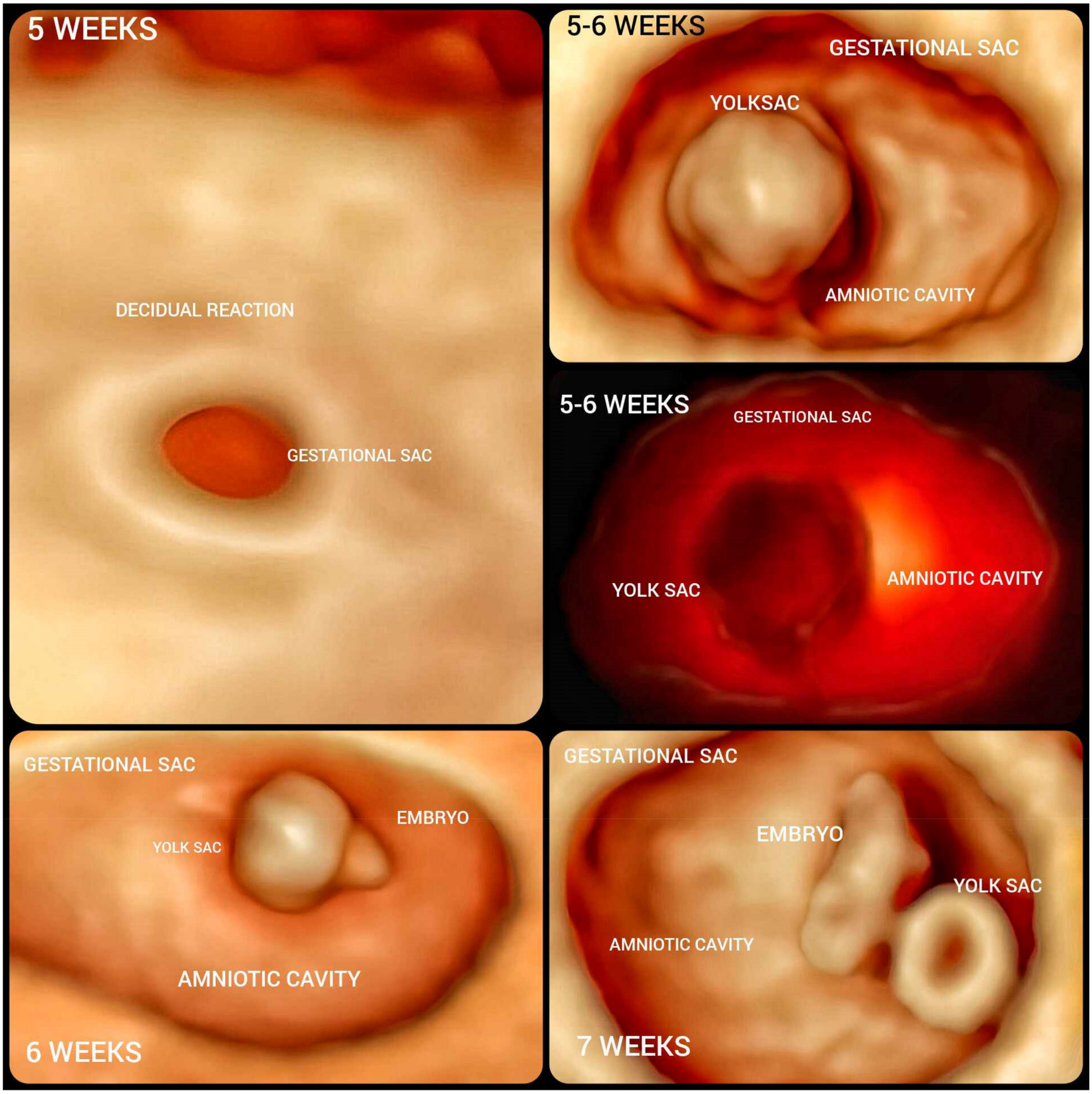

Figure 6: This series of 4D ultrasound images captures key stages in early pregnancy, beginning with the gestational sac and progressing to the yolk sac and a detectable embryonic heartbeat by 6–7 weeks. Within the framework of Barker's Hypothesis, these milestones signify critical periods of vulnerability when maternal stress, health status, and environmental exposures can profoundly influence fetal epigenetic programming. The early visibility of the heartbeat highlights the sensitivity of cardiovascular development to maternal factors, potentially elevating long-term risks of conditions like heart disease. This observation reinforces the necessity of early prenatal care and proactive maternal health management to reduce adverse programming effects.

Chronic disease risk: from early-life exposures to preventive strategies

Adverse early-life exposures, such as maternal malnutrition, stress, and environmental toxins, have been linked to long-term risks for chronic diseases, including type 2 diabetes, cardiovascular disorders, and obesity [2, 5, 17]. These risks arise from short-term fetal adaptations, such as altered glucose metabolism, which optimize survival during gestation but create long-term vulnerabilities when postnatal environments differ significantly from prenatal conditions [6, 16].

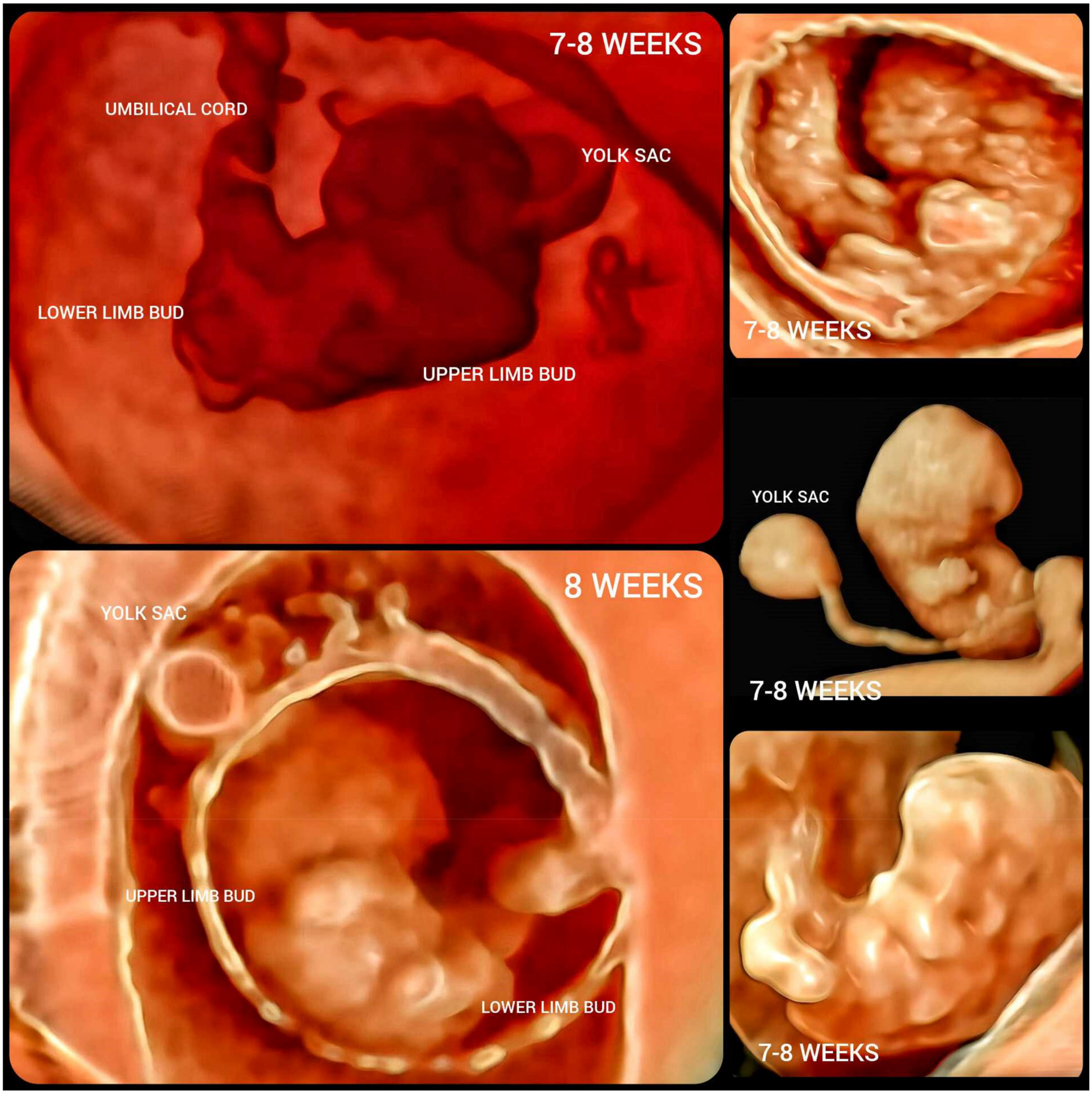

Figure 7: This set of 4D ultrasound images, taken at 7–8 weeks of gestation, illustrates the emergence of early anatomical features such as limb buds, a pulsating heart, and the first observable fetal movements. According to Barker's Hypothesis, these developmental milestones mark crucial phases during which maternal nutrition, stress levels, and overall health can shape fetal epigenetic programming. The observed cardiac activity and early movements signify the rapid growth of neuromuscular and cardiovascular systems, which are particularly susceptible to external and maternal influences at this stage. Adverse conditions can trigger epigenetic changes, heightening the risk of chronic illnesses and developmental issues later in life. This emphasizes the importance of maintaining optimal maternal health during this formative period.

Structural and functional changes in vital organs, such as the heart, pancreas, and kidneys, can limit their capacity to meet future metabolic demands, increasing the risk of chronic diseases [17, 32]. Prenatal stress primes the fetal immune system toward a pro-inflammatory state, which persists postnatally and contributes to conditions like atherosclerosis and metabolic syndrome [11, 22]. Catch-up growth following fetal growth restrictions exemplifies how mismatches between prenatal and postnatal environments amplify metabolic risks [32, 47].

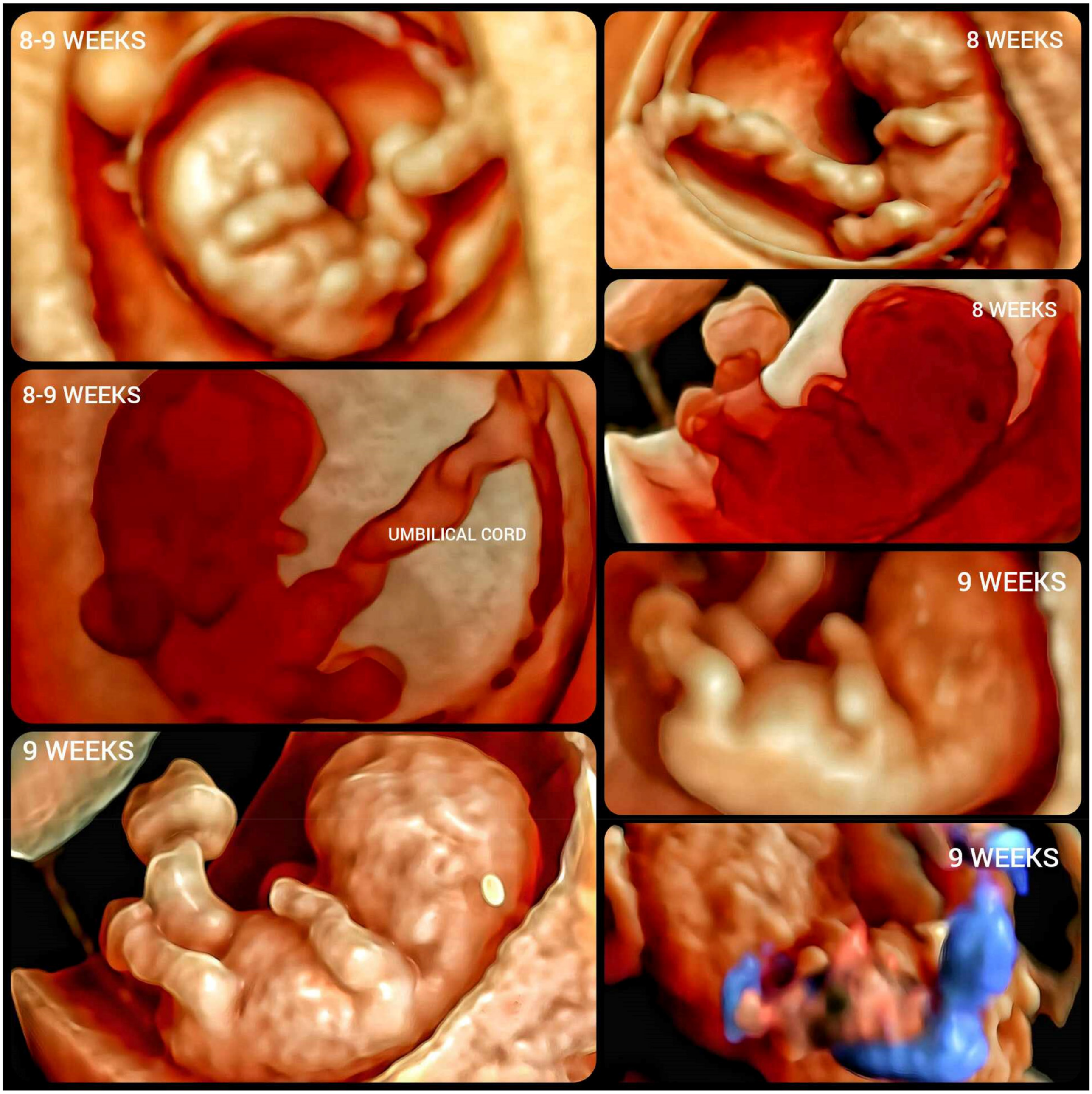

Figure 8: This series of 4D ultrasound images, taken between 8 and 9 weeks of gestation, reveals advanced anatomical formation, including clearly discernible hands, feet, a beating heart, and increasingly dynamic fetal movements. Barker's Hypothesis identifies this timeframe as a pivotal stage in fetal programming, during which maternal health, environmental exposures, and nutrition critically influence the maturation of essential organ systems. The observed growth and activity highlight the accelerated development of neurological and musculoskeletal systems, which remain highly vulnerable to maternal factors such as stress and dietary deficiencies. Adverse conditions during this phase may provoke epigenetic alterations, with potential long-term impacts on cardiovascular health, metabolic stability, and neurodevelopment.

Preventive strategies, including improved maternal nutrition, stress management, and targeted interventions, have shown promise in mitigating the long-term effects of adverse prenatal exposures [16, 46]. Biomarkers derived from epigenetic research enable precision medicine approaches by identifying individuals at high risk and tailoring interventions accordingly [20, 24]. These interventions underscore the importance of multidisciplinary care that integrates maternal, neonatal, and pediatric support to disrupt intergenerational cycles of poor health [44].

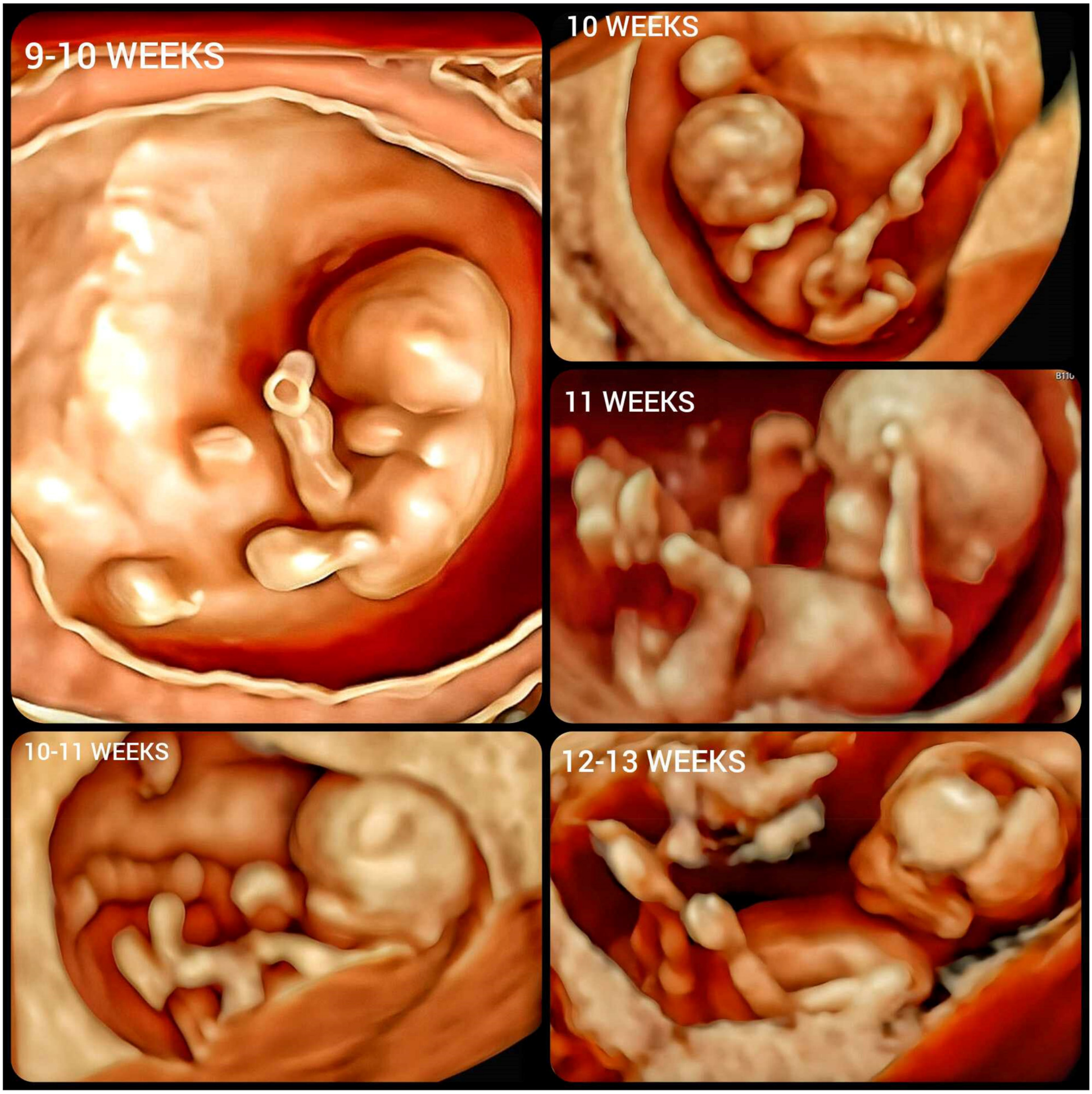

Figure 9: The 4D ultrasound images captured between 9 and 13 weeks showcase the fetus's fully developed anatomical features and dynamic movements, underscoring the importance of this critical developmental period. Barker's Hypothesis identifies this stage as foundational, where maternal well-being, environmental influences, and genetic predispositions play a vital role in shaping fetal epigenetic programming. The observed intricate movements and organ formation highlight the heightened sensitivity of the neural, cardiovascular, and musculoskeletal systems to factors such as maternal nutrition, stress, and exposure to environmental toxins. This phase is also significant for first-trimester evaluations, including non-invasive prenatal testing (NIPT), which offers vital information about genetic and epigenetic risks. These findings underscore the necessity of comprehensive maternal care to reduce the likelihood of long-term adverse health outcomes for the offspring.

Table 1: Fetal behavioral assessment indicators by development stage.

Stage	Key indicators	Additional notes
First trimester	Heart rate variability, limb movements, primitive reflexes	Basic motor activity and nervous system development begin.
Second trimester	Facial expressions, coordinated movements, sensory organ responsiveness	Signs of sensory development and muscle coordination appear.
Third trimester	Cognitive patterns, neural responses, active sleep-wake cycles	Advanced brain activity and preparation for postnatal adaptation.

Table 2: Maternal stressors, epigenetic changes, and health outcomes.

Maternal stressors	Epigenetic changes	Health outcomes	Additional notes
Poor nutrition	DNA methylation patterns, histone modifications	Cardiovascular risk, preterm birth	Inadequate nutrients disrupt fetal growth and organ formation.
Psychological stress	Altered cortisol response, telomere shortening	Neurodevelopmental disorders, behavioral issues	Chronic stress affects fetal stress regulation and brain development.
Exposure to toxins	Impaired HPA axis, oxidative stress markers	Metabolic syndrome, immune dysfunction	Environmental toxins alter cellular functions and increase inflammation.

Revolutionizing prenatal care: integrating Barker's Hypothesis, NIPT, and AI-driven 4D ultrasound

Integrating the Barker's Hypothesis with advanced technologies, such as non-invasive prenatal testing (NIPT) and AI-powered 4D ultrasound, is transforming prenatal care [24, 26]. NIPT allows for the safe and accurate detection of genetic abnormalities through the analysis of cell-free fetal DNA, reducing the need for invasive procedures [30, 49]. AI-powered 4D ultrasound enhances diagnostic capabilities by providing dynamic, real-time imaging of fetal anatomy and development, facilitating early detection of structural anomalies [31, 33].

AI algorithms analyze complex datasets from imaging, Doppler studies, and maternal health data to detect abnormalities in placental function, fetal circulation, and neurodevelopment [41, 48]. As illustrated in Figure 2, predictive models that integrate genetic and environmental markers play a crucial role in identifying high-risk pregnancies and guiding the management of complications like preeclampsia or preterm birth, enabling timely and targeted interventions [47, 50]. These technologies improve prenatal outcomes, particularly in resource-limited settings, where scalable AI-driven diagnostic tools can bridge healthcare gaps (Figure 10) [46, 51].

AI-driven prenatal diagnostics also present ethical considerations, including algorithmic transparency and the need to validate models across diverse populations [45, 52]. Collaborative efforts among clinicians, engineers, and policymakers are crucial to developing evidence-based guidelines and promoting equitable access to these advanced technologies [53]. As prenatal care increasingly integrates AI, it holds promise for addressing global health disparities and optimizing long-term outcomes for future generations [54] (Figures 11 and 12).

Discussion

Improving accessibility of technical concepts in prenatal research: simplifying complex jargon with practical recommendations

This section reinterprets technical terms and concepts central to understanding prenatal development and its lifelong implications, ensuring accessibility for readers less familiar with the subject. Simplified explanations, relatable analogies, and practical recommendations are used while maintaining scientific integrity.

Epigenetics and gene regulation

Epigenetics encompasses processes such as DNA methylation and histone acetylation, which regulate gene activity without altering the underlying DNA sequence [10, 12]. These mechanisms can be likened to molecular "switches" that turn genes on or off depending on environmental signals. For example, inadequate nutrition during pregnancy can activate genes promoting immediate survival but inadvertently increase the likelihood of chronic conditions like diabetes later in life [14, 17]. This concept demonstrates how the prenatal environment leaves lasting imprints on biological systems.

Developmental adaptations and trade-offs

Terms like neurogenesis (brain development), immune maturation (immune system development), and metabolic reprogramming (energy system adjustments) describe processes that adapt to prenatal conditions [5, 6]. For instance, if resources are limited, the fetus may prioritize brain development over other systems, such as muscle growth, to

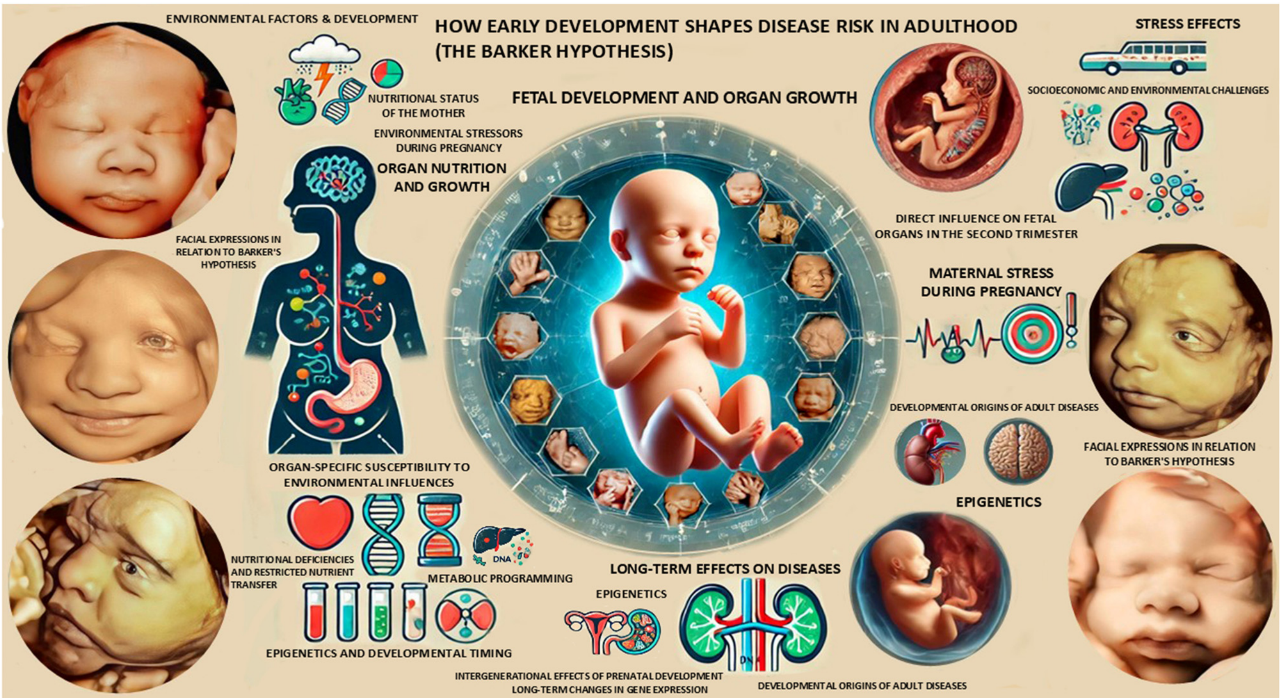

Figure 10: This diagram integrates Barker's Hypothesis with cutting-edge 4D ultrasound and AI technologies to illustrate how early fetal development shapes adult disease risk. It highlights the profound influence of maternal stress, diet, and environmental factors on fetal growth and epigenetic modifications, which affect the functionality of organs and overall health outcomes in later life. Real-time visualization provided by 4D ultrasound captures fetal movements and facial expressions, offering valuable insights into neurodevelopment and physiological health. These observations facilitate the early detection of chronic disease risks, including cardiovascular and metabolic disorders, by analysing organ-specific developmental patterns influenced by maternal conditions. This integrated framework underscores the critical role of early maternal-fetal health monitoring and timely interventions in reducing lifelong health risks.

ensure survival [14, 16]. However, these adaptations often come with trade-offs, predisposing individuals to metabolic issues as adults [2].

Mismatch hypothesis and environmental adaptation

The mismatch hypothesis explains how physiological adjustments made in response to prenatal conditions can become maladaptive if the postnatal environment differs significantly [1, 5]. A fetus exposed to scarcity may develop a metabolism optimized for resource-poor conditions. If later exposed to a calorie-rich environment, this mismatch increases risks of obesity and cardiovascular diseases [16]. An analogy would be designing a vehicle for rugged terrain and using it on smooth highways, where its features may no longer serve its purpose effectively.

Advanced technologies in prenatal care

Innovations such as AI-powered 4D ultrasound, deep learning, and Doppler studies are reshaping prenatal care. AI-enhanced 4D ultrasound provides dynamic, real-time imaging of fetal development, enabling the detection of anomalies earlier than traditional 2D imaging [31, 33]. Deep learning algorithms, or advanced computer programs that identify patterns in large datasets, enhance diagnostic precision [41, 43]. Doppler studies, which assess blood flow between mother and fetus, are simplified as tools to monitor how well oxygen and nutrients are delivered to the baby [30, 32].

Mechanisms of fetal programming

Key terms like the hypothalamic-pituitary-adrenal axis (HPA), placental efficiency, and neuroendocrine pathways describe how the fetal environment influences stress and resource availability [5, 14]. These can be reframed as "the body's stress regulation system," "the effectiveness of the placenta in nourishing the baby," and "maternal stress signals affecting fetal development," respectively [30, 32]. For instance, heightened maternal anxiety can recalibrate the fetal stress response system, predisposing the child to heightened sensitivity to stress in later life [18].

Figure 11: This diagram highlights various fetal facial expressions, including yawning, smiling, frowning, and hand movements, as captured through AI-enhanced 4D ultrasound during the third trimester. These expressions reflect significant advancements in behavioural and neural development, indicating the maturation of sleep-wake patterns, emotional responses, and neural systems. In line with Barker's Hypothesis, these observed behaviours mark the outcome of epigenetic programming shaped by maternal stress, health, and environmental conditions throughout pregnancy. Such expressions suggest the fetus's preparedness for life outside the womb, with disruptions during this stage potentially leading to neurodevelopmental or behavioural challenges later in life. AI-driven analysis of these patterns enables the early detection of abnormalities, facilitating timely interventions to address risks influenced by prenatal factors.

Ethical and societal considerations

Concepts such as algorithmic transparency, inclusivity, and bias address the ethical challenges of AI in prenatal care. Algorithmic transparency ensures the workings of AI models are understandable and verifiable [45, 53]. Inclusivity focuses on ensuring technology works effectively for diverse populations, while bias refers to unintended favoring of certain groups [52]. Addressing these issues is critical for equitable prenatal care.

Linking early-life conditions to chronic disease risk

Oxidative stress, low-grade inflammation, and vascular integrity are technical terms often used to describe the biological underpinnings of chronic disease risk [11, 14]. These can be simplified as "damage caused by harmful molecules," "persistent low-level immune activity," and "the health of blood vessels," respectively [16, 17]. For example, poor maternal nutrition during pregnancy can increase oxidative stress in the fetus, impairing vascular development and raising the risk of heart disease in adulthood [5].

By translating these intricate scientific terms into more relatable language and providing practical examples, the research becomes more accessible. This approach ensures a broader audience can engage with and apply the findings, enhancing their impact on public health and clinical practices.

Comprehensive benefits of 4D ultrasound in prenatal diagnostics

4D ultrasound represents a transformative advancement in prenatal care by offering real-time, dynamic imaging that surpasses the limitations of traditional 2D and 3D techniques [27, 28]. Unlike static 2D images or reconstructed 3D stills, 4D ultrasound incorporates the dimension of time, allowing continuous observation of fetal behaviors such as yawning, swallowing, and stretching [33, 34]. These dynamic visualizations provide critical insights into neurodevelopmental and motor functions, which are essential indicators of fetal health [29, 31].

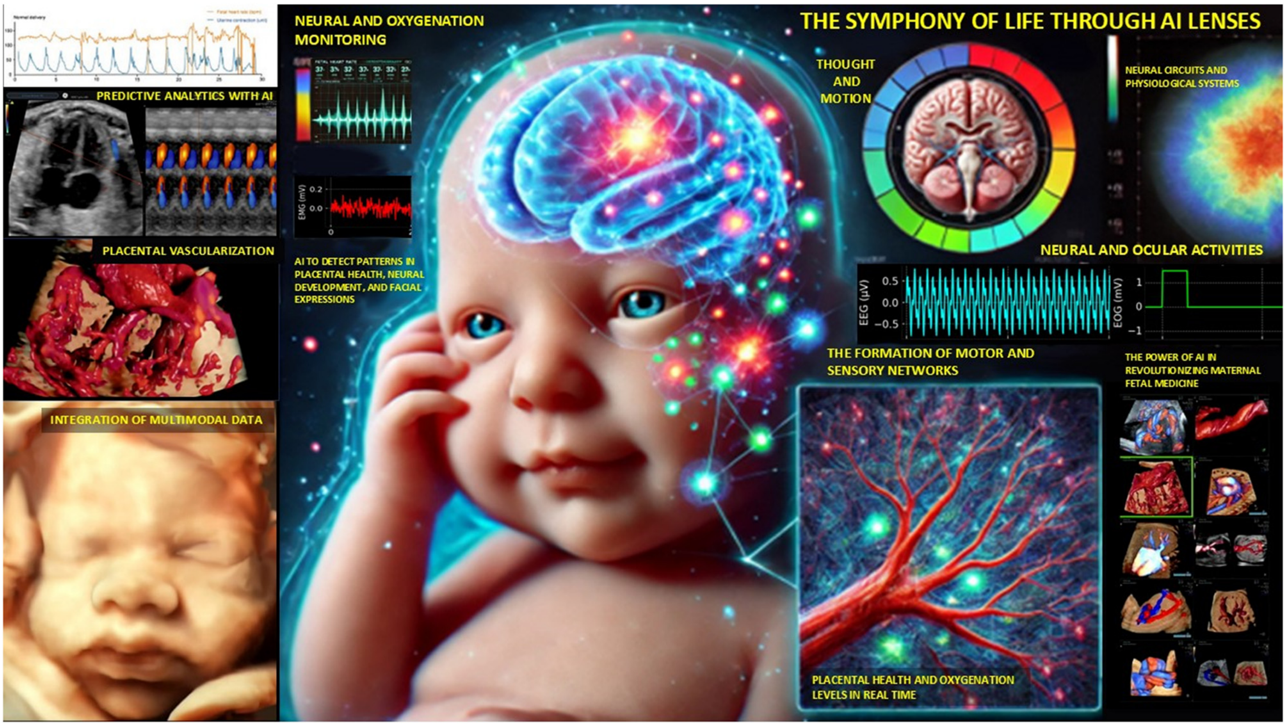

Figure 12: This illustration depicts the intricate dynamics of fetal development through AI-enhanced 4D imaging, highlighting the coordination between neural and physiological processes during pregnancy. The baby's peaceful facial expressions and highlighted brain overlay symbolize synchronized neural activity, the growth of motor-sensory networks, and effective oxygenation. Doppler waveforms and placental vascularization emphasize the placenta's critical function in providing nutrients and oxygen, aligning with Barker's Hypothesis that prenatal conditions shape lifelong health outcomes. Real-time monitoring of neural and ocular functions, alongside vascular flow analysis, showcases the integration of reflexes and core physiological systems. By combining these AI-derived insights, maternal-fetal medicine is transformed, offering accurate risk evaluations and enabling early, tailored interventions to improve health trajectories.

Beyond movement analysis, the enhanced spatial and temporal resolution of 4D ultrasound enables precise detection of structural anomalies, including facial clefts, limb deformities, and cardiac defects [30, 35]. Early identification of such conditions allows for timely interventions, improving pregnancy outcomes [36]. Equally significant is the technology's role in assessing placental function. Through real-time Doppler imaging, clinicians can monitor placental blood flow dynamics, crucial for detecting risks such as intrauterine growth restriction (IUGR) and pre-eclampsia [37, 38]. In high-risk pregnancies, 4D ultrasound offers a comprehensive evaluation of fetal well-being, identifying subtle markers of distress or neuromotor delays [55]. The technology also promotes parental engagement by allowing real-time observation of fetal movements, fostering emotional bonding and enhancing adherence to prenatal care recommendations [39, 56]. Collectively, these benefits highlight 4D ultrasound as a powerful tool for enhancing diagnostic accuracy and improving clinical decision-making [39].

Integrating AI and 4D ultrasound: expanding diagnostic precision

The integration of artificial intelligence (AI) with 4D ultrasound enhances its diagnostic capabilities by enabling advanced data analysis, which surpasses the limits of human interpretation [42, 43]. AI-powered applications such as the Kurjak Antenatal Neurodevelopmental Test (KANET) leverage real-time imaging to detect subtle motor and facial irregularities, which may signal neurodevelopmental disorders like cerebral palsy or autism spectrum disorders [35, 39]. By combining imaging with epigenetic data, AI uncovers the complex interplay between genetic predispositions and environmental exposures during gestation [48]. For example, biomarkers influenced by DNA methylation or histone modifications can be tracked to assess the impacts of maternal stress or placental dysfunction [14, 17].

Predictive models further amplify AI's role by integrating maternal health data, fetal neurobehavioral indicators, and physiological parameters to construct risk profiles for conditions such as preeclampsia, intrauterine growth restriction, and preterm birth [47, 57]. These models facilitate early detection and personalized interventions tailored to individual risk factors [51]. AI also supports longitudinal monitoring, offering continuous insights into how early prenatal exposures influence long-term health outcomes [53, 58]. In resource-limited settings, portable AI-enhanced 4D ultrasound systems bridge healthcare disparities by automating data interpretation and ensuring consistent diagnostics across diverse clinical environments [44, 46]. Together, AI and 4D ultrasound provide a dynamic approach to prenatal care, transitioning from reactive treatments to proactive, personalized interventions [59].

Enhancing diagnostic precision: AI's role in modern prenatal care

Artificial intelligence is transforming prenatal diagnostics by automating complex analyses and providing actionable insights that improve diagnostic precision [41, 60]. Machine learning models excel in detecting neurodevelopmental delays and structural anomalies with accuracy levels that often surpass traditional techniques [61]. By integrating maternal health records, genetic profiles, and imaging features, predictive analytics identify early risks for complications such as preeclampsia and chromosomal anomalies, allowing for timely interventions [52, 57].

AI also enhances real-time monitoring of fetal behaviors, including coordinated limb movements and rhythmic breathing, which serve as critical biomarkers for early developmental assessments [39, 42]. Automated segmentation tools driven by AI streamline the analysis of fetal anatomy, improving consistency in detecting anomalies such as vascular defects and cardiac malformations [61]. This automation not only alleviates the cognitive burden on clinicians but also democratizes access to high-quality diagnostics through telemedicine platforms and portable devices [44, 46]. By addressing diagnostic variability and expanding access, AI helps bridge the gap between traditional and modern prenatal care models, ensuring more equitable healthcare delivery globally [53].

The role of AI in the study of the fetal heart

Artificial intelligence (AI) has significantly advanced the precision of fetal cardiology by enhancing diagnostic capabilities and streamlining clinical workflows. Studies provide valuable insights into the transformative role of AI in assessing fetal cardiac structure and function.

(1) Enhancing diagnostic accuracy: AI algorithms, such as Heartassist™, have demonstrated their ability to automatically assess the quality of fetal cardiac views during the second trimester [52, 57, 61]. By minimizing variability among operators and ensuring consistent evaluation, these tools facilitate the early detection of congenital heart defects (CHDs), including ventricular septal defects and complex anomalies [52].
(2) Functional and structural analysis: The integration of AI with imaging techniques like Doppler and 4D ultrasound has improved the ability to analyze fetal heart dynamics [57, 59, 61]. AI helps detect subtle changes in blood flow patterns and cardiac geometry that are challenging to identify with conventional methods [61].
(3) Workflow optimization: AI tools prioritize high-risk cases and reduce the time spent on manual assessments, enabling clinicians to focus on decision-making [44, 46, 51]. This streamlined approach is critical for addressing high patient volumes while maintaining quality care [51].

By leveraging AI-driven tools, clinicians can achieve earlier, more accurate diagnoses and improve prenatal care outcomes [50]. The integration of AI into fetal heart studies not only advances research but also ensures equitable and effective care delivery [62].

Revolutionizing healthcare through AI: case studies and emerging innovations

The integration of artificial intelligence (AI) in healthcare is driving unprecedented improvements in decision-making, patient empowerment, and care coordination, demonstrating its transformative potential across various domains. AI tools are poised to address communication gaps by offering patients tailored insights, personalized recommendations, and improved access to medical resources [48, 60]. For example, an AI-powered Healthcare Assistant App could integrate health IT interoperability, price transparency, and user-centered design, simplifying processes like scheduling, provider selection, and navigating costs. By providing patients with customized health advice and access to real-time information, such innovations empower them to make informed decisions and take more control of their healthcare journey [52].

However, achieving widespread adoption of AI tools presents challenges such as data privacy, inclusivity, and trust-building. Addressing these concerns requires transparent data-sharing practices, equitable design principles, and culturally tailored communication [45]. For example, developing low-literacy interfaces and ensuring device compatibility can enhance access for underserved populations [44]. Recent case studies have shown that patient-centric AI solutions improve care delivery when designed inclusively. For instance, AI-driven platforms in OB/GYN settings have led to better maternal and fetal outcomes through predictive analytics and tailored interventions [59].

A key area of AI success involves video generation technologies, where advanced text-to-video (T2V) models such as OpenAI's Sora Turbo and Google's Veo 2 have emerged. These technologies have demonstrated significant potential in patient education, medical training, and telemedicine [62]. For example, customized AI-generated videos can be used to educate patients on surgical procedures, enhancing their understanding and compliance [62]. Similarly, in training settings, AI-generated simulations offer standardized and scalable learning experiences for medical professionals, reducing knowledge variability and improving skills retention [62]. Despite these benefits, concerns regarding misinformation, privacy breaches, and the authenticity of AI-generated content must be addressed through regulatory safeguards and real-time deepfake detection mechanisms [59].

In obstetrics and gynecology, AI is playing a critical role in transforming prenatal care and diagnostic imaging. AI applications in 3D/4D ultrasound imaging have enhanced the accuracy and consistency of fetal facial profile analysis, leading to earlier and more precise diagnoses of anomalies [42]. Similarly, in the prediction of high-risk conditions like preeclampsia, AI models have outperformed traditional methods by offering more reliable and timely risk assessments [47]. Expanding and validating these AI models across diverse populations is crucial to ensure their effectiveness and equity [50].

The European Union and other international organizations have issued guidelines to regulate AI integration, ensuring that it enhances care while mitigating risks related to errors or misuse [50]. Moving forward, interdisciplinary collaboration among technologists, clinicians, and policymakers is essential for scaling AI solutions globally while addressing barriers to adoption [44]. By fostering this collaboration, AI has the potential to bridge communication gaps, improve patient outcomes, and optimize decision-making in healthcare [52].

Addressing ethical considerations and validation challenges

While AI-powered 4D ultrasound offers remarkable potential, several ethical and practical challenges must be addressed to ensure safe and equitable deployment. One major concern involves algorithmic bias, which can arise when AI models are trained on non-representative datasets [53]. Such biases may result in diagnostic inaccuracies, particularly for underrepresented populations [46]. Ensuring dataset diversity and conducting external validations across different demographics are crucial to mitigating this risk [44].

Transparency and interpretability of AI models are equally important, as clinicians need clear explanations of how diagnostic predictions are generated [45]. This transparency fosters trust and supports informed decision-making [45]. Protecting patient data privacy is another critical issue, especially when sensitive maternal and fetal information is involved [52]. Secure data governance frameworks and decentralized data analysis methods, such as federated learning, can safeguard privacy while enabling collaborative research [53].

Validation in real-world clinical settings is essential to bridge the gap between experimental success and practical application [50]. Differences in equipment, clinical protocols, and patient demographics can affect AI performance, making external validation and prospective trials necessary [51]. By addressing these challenges, stakeholders can ensure that AI-driven prenatal diagnostics remain reliable, unbiased, and ethically sound, fostering global adoption and improving long-term maternal and fetal health outcomes [59].

Bridging research and policy: leveraging maternal and child health programs to address DOHaD implications through AI integration

The integration of artificial intelligence (AI) into maternal and child health programs is transforming the way we understand and address early-life health risks. Guided by the Developmental Origins of Health and Disease (DOHaD) framework, which emphasizes the lasting impact of early-life exposures on long-term health, AI offers a critical opportunity to intervene during key developmental windows [5]. By incorporating advanced imaging technologies and machine learning, AI is paving the way for early interventions designed to mitigate chronic disease risks and support equitable healthcare systems globally.

AI-powered imaging tools, such as 4D ultrasound, are revolutionizing prenatal diagnostics. These technologies enable the early detection of fetal abnormalities, placental dysfunction, and developmental delays that would otherwise go unnoticed using conventional methods [24–26]. Machine learning algorithms, capable of analyzing vast datasets over time, can identify biomarkers related to fetal brain development, vascular health, and placental function, offering valuable insights into potential risks [42]. These early warnings allow clinicians to tailor interventions that optimize care for both the mother and fetus, helping to improve long-term outcomes.

As AI integrates more deeply into maternal health systems, its benefits extend beyond individual diagnoses. Adaptive AI-driven care models are reshaping population health by addressing disparities in access to prenatal diagnostics, especially in resource-limited regions [46, 53]. Portable AI-enabled imaging devices, combined with telemedicine, bring advanced diagnostic capabilities to underserved communities, reducing maternal and neonatal mortality rates in areas where access to traditional healthcare services is limited. These innovations provide a more equitable distribution of care, ensuring that vulnerable populations receive the same diagnostic precision as those in more affluent settings.

Policy development plays a critical role in maximizing AI's potential within maternal and child health programs. Policymakers can use AI's ability to synthesize complex, longitudinal data to design interventions aimed at preventable risks [2, 6]. For example, data linking maternal stress, poor nutrition, and environmental hazards to adverse birth outcomes provide a foundation for targeted public health measures. By addressing these underlying risks during pregnancy and infancy, policymakers can help break intergenerational cycles of poor health and reduce the burden of preventable diseases.

However, as AI becomes embedded in prenatal care, ethical concerns must be addressed to ensure its implementation benefits all populations equitably. One major concern is the potential for bias in AI models, which arises when training datasets lack representation from diverse populations [51]. Inaccurate predictions and misdiagnoses can result if AI systems are not properly validated across various demographic and environmental contexts. For example, diagnostic tools trained on data from high-income settings may underperform in rural or low-resource regions. To mitigate this risk, developers must prioritize dataset diversity and validate algorithms on populations with varied genetic, socioeconomic, and geographic backgrounds.

Privacy concerns surrounding the use of sensitive maternal and fetal data further complicate AI adoption. Ensuring patient confidentiality while allowing for large-scale data analysis requires robust safeguards, such as encryption and decentralized data-sharing models [46]. Federated learning, which enables AI models to learn from data stored locally without transferring it, offers a promising solution by preserving privacy while maintaining diagnostic accuracy. By building trust through secure data-handling practices, healthcare systems can foster greater acceptance of AI among both clinicians and patients.

To establish trust and reliability, AI technologies require rigorous validation before widespread deployment. Robust validation involves training and testing AI models on datasets that reflect diverse populations, minimizing the risk of biased outcomes [57, 61]. Cross-population testing, where models are evaluated using external datasets from different regions, ensures generalizability and broad applicability. Longitudinal studies that track fetal health over time are particularly valuable, as they allow AI systems to predict long-term outcomes based on early biomarkers. In parallel, real-world validation trials help assess the practical performance of AI tools in clinical settings, ensuring they can be effectively integrated into routine prenatal care.

Equipping clinicians with the necessary skills to interpret and apply AI-generated insights is another key aspect of successful implementation [63]. Many clinicians currently lack experience with AI-powered tools, making comprehensive training programs essential [59]. Incorporating AI modules into medical school curricula and providing continuing education opportunities help bridge this gap. Workshops, simulations, and hands-on training sessions further ensure that healthcare providers feel confident in using AI to enhance decision-making [63].

In addition to training, robust infrastructure is needed to support AI integration in clinical workflows. In high-resource settings, hospitals can leverage existing data systems and advanced imaging technologies to seamlessly incorporate AI. In low-resource settings, portable devices and cloud-based platforms offer scalable solutions. Cloud-based analysis allows clinicians in remote areas to access real-time diagnostic support, creating a network of interconnected facilities that share AI-generated insights. Public-private partnerships and strategic investments are critical in ensuring that these technologies are affordable and accessible to all.

Despite its promise, AI faces challenges related to interpretability, bias, and privacy, which must be addressed through collaboration between technologists, clinicians, policymakers, and ethicists [51]. Regulatory frameworks should establish clear guidelines for the ethical use of AI in prenatal care, focusing on transparency, fairness, and the protection of patient autonomy. Misuse of genetic or epigenetic data for discriminatory purposes must be strictly regulated, with appropriate safeguards in place to prevent stigmatization or overmedicalization of at-risk populations [60].

Interdisciplinary collaboration will be key to overcoming these challenges and ensuring that AI achieves its full potential [51, 60]. Policymakers, healthcare leaders, and industry stakeholders must work together to develop AI systems that are not only technically sound but also culturally sensitive and adaptable to diverse healthcare environments. Community involvement is equally important, as public awareness campaigns can help build trust in AI-driven healthcare solutions and encourage their acceptance.

By addressing the social determinants of health – such as maternal stress, poor nutrition, and environmental hazards – alongside technological innovations, AI can have a profound impact on intergenerational health outcomes [1]. Shifting prenatal care from reactive treatments to proactive, preventive models will empower families and clinicians with the knowledge needed to support lifelong health. AI's role in synthesizing complex data makes this shift possible, offering actionable insights that guide early interventions with long-term benefits.

As AI continues to evolve, its integration into maternal and child health programs represents a major milestone in global health policy. With sustained investment, ethical oversight, and equitable implementation, AI has the potential to reduce disparities, improve maternal and neonatal outcomes, and contribute to societal transformation. By combining cutting-edge technology with thoughtful policy, maternal and child health programs can become a model for predictive, personalized, and preventive care, reshaping health trajectories for generations to come.

Limitations of AI in obstetrics

While artificial intelligence (AI) holds immense potential in advancing prenatal diagnostics, several limitations hinder its widespread adoption and integration into obstetric care. Sarno et al. have outlined critical barriers that must be addressed to fully realize the benefits of AI in this field [51, 52]:

(1) **Data quality and diversity:** The accuracy of AI models depends on access to large, high-quality, and diverse datasets. However, many existing datasets lack representation of diverse populations, leading to potential biases in diagnostic outcomes. This limits the generalizability of AI systems across different demographics and clinical settings [44, 53, 58].
(2) **Transparency and interpretability:** Many AI models operate as "black boxes," offering little insight into how predictions and decisions are made. This lack of transparency poses challenges for clinical adoption, as clinicians may hesitate to rely on systems they cannot fully understand or explain to patients [52, 59].
(3) **Integration with clinical workflows:** Seamlessly incorporating AI tools into existing workflows, including electronic health records (EHRs), remains a technical challenge. Issues such as interoperability and the need for staff training further complicate the adoption process, especially in resource-constrained environments [41, 46].
(4) **Ethical and privacy concerns:** The use of patient data in AI systems raises ethical concerns regarding consent, privacy, and security. Robust data governance frameworks are essential to ensure compliance with regulatory standards and maintain patient trust [45, 48, 53].
(5) **Validation and real-world testing:** Many AI tools are validated in controlled experimental settings but face challenges when applied in real-world clinical environments. Differences in equipment, protocols, and patient populations can lead to variability in performance, highlighting the need for rigorous external validation before widespread implementation [46, 51, 52].

Addressing these limitations requires collaboration among researchers, clinicians, and policymakers to develop solutions that prioritize equity, transparency, and real-world applicability. Only through such efforts can AI achieve its transformative potential in obstetrics.

Conclusions

This study highlights the transformative integration of the Barker's Hypothesis with advanced technologies, specifically artificial intelligence (AI)-driven 4D ultrasound, in modern prenatal care. By emphasizing how early-life conditions profoundly shape lifelong health through mechanisms like epigenetic programming, the research underscores the potential of AI to revolutionize healthcare. AI's ability to synthesize maternal health data, genetic markers, and imaging findings enables predictive models that improve early identification and management of conditions such as preeclampsia and neurodevelopmental disorders. Non-invasive prenatal testing (NIPT) and real-time 4D ultrasound provide safe and precise diagnostic tools, reducing risks and enhancing intervention strategies.

The manuscript advocates for a shift from reactive to preventive healthcare, focusing on the first 1,000 days as a critical intervention period. Expanding access to these advanced technologies in resource-limited settings is essential for promoting health equity. Ethical concerns, including the need for algorithmic transparency and inclusivity, are addressed to ensure responsible application across diverse populations. These considerations are key to the equitable and effective implementation of AI-enhanced prenatal care.

Future research should explore the transgenerational effects of early-life interventions and refine AI algorithms for broader applicability. Policymakers are encouraged to integrate these technologies into routine prenatal care through strategies emphasizing affordability, education, and global accessibility. By combining predictive analytics with multidisciplinary collaboration, this framework has the potential to reduce the prevalence of chronic diseases and enhance maternal and child health outcomes. Ultimately, these innovations lay the foundation for healthier generations, creating a transformative impact on global health.

Acknowledgments: The authors appreciate the Indonesian Society of Obstetrics and Gynecology (POGI) and the Indonesian Society of Maternal-Fetal Medicine (HKFM) for encouraging and supporting the work of this review article. The authors would like to extend their heartfelt gratitude to Henry Herculanus Iman Kalis for his invaluable insights and contributions, which have significantly enriched the understanding and advancement of this work in the fields of artificial intelligence and information technology.
Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interests: The authors state no conflict of interest.
Research funding: None declared.
Data availability: Not applicable.

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