ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

# Gene–Nutrient Interactions and Maternal-Fetal Health in Sub-Saharan Africa: Current Evidence and Future Policy Directions

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Publication Date: 2026/08/18

**Abstract: In Sub-Saharan Africa (SSA), maternal and fetal health remains threatened by high rates of maternal mortality, micronutrient deficiencies, anemia, low birth weight, preterm birth and childhood stunting. The study of interactions between nutrients and the genome, known as nutrigenomics, has emerged as a promising approach to understand biological variability in pregnancy outcomes and to advance precision nutrition. Nevertheless, data from African populations are still scarce, despite the region's exceptional genetic diversity and heavy burden of maternal and child health problems related to nutrition. A narrative review was performed to synthesize current evidence on gene-nutrient interactions and their implications for maternal-fetal health in SSA. Literature published in the English language from January 2010 to July 2026 was identified through searches of PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. These searches were complemented by screening reference lists and reports from international organizations. Eligible publications included original research articles, systematic reviews, meta-analyses, randomized controlled trials, cohort studies and policy documents that related to nutrigenomics, nutrigenetics, epigenetics, maternal nutrition, fetal development and precision nutrition. Evidence was thematically synthesized. This review shows that maternal nutrition and genetic variation can interact to impact pregnancy outcomes through mechanisms related to folate metabolism (MTHFR), iron metabolism (HFE), vitamin D signaling (VDR), micronutrient metabolism and nutrition-sensitive epigenetic regulation. The Developmental Origins of Health and Disease (DOHaD) paradigm suggests that maternal nutritional exposures during critical developmental windows influence fetal programming via DNA methylation, histone modification, and other epigenetic processes . Current nutrigenomic evidence from SSA remains geographically limited and hampered by poor genomic infrastructure, lack of funding, limited biobanking capacity, shortage of skilled researchers and underrepresentation of African populations in genomic databases. Nevertheless, progress in genomic technologies, digital health and artificial intelligence offer opportunities to advance precision nutrition research and develop context-specific maternal nutrition policies. Nutrigenomics has huge potential to improve maternal and fetal health in SSA using personalised nutrition approaches and evidence-based maternal health interventions. African-led nutrigenomics research, development of genomic infrastructure, promotion of regional collaboration and inclusion of gene–nutrient evidence in maternal health policies are necessary to improve pregnancy outcomes and reduce the long-term burden of nutrition-related diseases. Future investments in precision nutrition should prioritise African populations to equitably translate genomics advances to maternal and child healthcare.**

***Keywords:*** *Nutrigenomics; Nutrigenetics; Maternal Health; Fetal Development; Precision Nutrition; Gene Nutrient Interactions; Epigenetics; DOHaD; Sub Saharan Africa.*

**How to Cite:** Samuel Danley; Faith Dedan Nyari (2026) Gene–Nutrient Interactions and Maternal-Fetal Health in Sub-Saharan Africa: Current Evidence and Future Policy Directions. *International Journal of Innovative Science and Research Technology*, 11(8), 836-886. https://doi.org/10.38124/ijisrt/26aug359

## I. INTRODUCTION

➢ *Background*

Maternal and fetal health continue to be major public health concerns in Sub-Saharan Africa (SSA), a region that continues to bear a disproportionate burden of adverse pregnancy and birth outcomes despite global improvements in maternal and child health. Maternal health The health of women during pregnancy, childbirth and the post-natal period Fetal health The growth, development and survival of the fetus throughout gestation. Collectively, nutritional status, access to health services, socioeconomic conditions, and biological factors including genetic susceptibility and gene-environment interactions have a strong influence on these outcomes [1].

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

While considerable progress has been made worldwide in reducing maternal mortality in the last two decades, SSA remains the epicenter of avoidable maternal deaths. The World Health Organization (WHO) estimates that around 260,000 women died from complications related to pregnancy and childbirth in 2023, with Sub-Saharan Africa accounting for almost 70% of such deaths, or approximately 182,000 maternal deaths per year [1]. In many countries in SSA, the maternal mortality ratio is still far above the Sustainable Development Goal (SDG) target of less than 70 maternal deaths per 100,000 live births by 2030. Major causes of maternal mortality include severe hemorrhage, hypertensive disorders of pregnancy (e.g., preeclampsia and eclampsia), infections, complications during delivery, and unsafe abortions, many of which are preventable with timely interventions and adequate maternal nutrition [1].

Beyond maternal mortality, adverse fetal outcomes remain a major challenge throughout the region. LBW (birth weight <2,500 grams) is one of the leading causes of neonatal morbidity and mortality in SSA. There is evidence that poor maternal nutrition before conception and during pregnancy significantly increases the risk of low birth weight, intra-uterine growth restriction (IUGR), preterm birth and neonatal complications [2]. Low birth weight has also been associated with impaired cognitive development, increased susceptibility to infectious diseases in childhood, and higher risk of non-communicable diseases later in life [2].

Another major concern is childhood stunting. 5 This is associated with maternal nutritional deficiencies and poor intrauterine conditions. Stunting, which is defined as impaired linear growth resulting from chronic undernutrition, affects millions of children in SSA and often begins during fetal development and the first 1,000 days of life. Fetal growth restriction and childhood stunting are strongly linked to maternal undernutrition, inappropriate gestational weight gain, micronutrient deficiencies, recurrent infections, and low dietary diversity. These factors set up a vicious cycle of malnutrition, poverty, and poor health outcomes through the generations [3].

Micronutrient deficiencies are prevalent among pregnant women in SSA and are a major contributor to poor maternal-fetal health outcomes. Iron, folate, iodine, zinc, calcium, vitamin A and vitamin D deficiencies are especially common and have far-reaching effects on pregnancy outcomes. The most common cause of anemia in pregnancy is iron deficiency and it is associated with an increased risk of maternal death, premature delivery and low birth weight. Deficiency of folate is associated with neural tube defects, and insufficient consumption of iodine can negatively impact fetal brain development and cognitive ability. Calcium and vitamin D deficiencies have also been associated with hypertensive disorders of pregnancy and suboptimal fetal skeletal development [3].

Maternal nutrition plays a key role in fetal growth, development and lifelong health. Pregnancy is associated with increased nutritional requirements to support the growth of the placenta, development of fetal organs, expansion of maternal tissues, and metabolic adaptations. Therefore, adequate intake of energy, protein, essential fatty acids, vitamins and minerals is important for optimizing maternal and neonatal outcomes. UNICEF explains that poor maternal diets deficient in important nutrients such as iron, folate, calcium, iodine, and zinc are associated with anemia, preeclampsia, hemorrhage, stillbirth, low birth weight, developmental delays, and higher maternal mortality [3]. Emerging evidence also supports that maternal nutritional exposures may influence fetal gene expression through epigenetic mechanisms, which would be consistent with the developmental origins of health and disease (DOHaD) hypothesis and the relevance of gene-nutrient interactions during pregnancy.

With the current burden of maternal mortality, low birth weight, stunting and micronutrient deficiencies in SSA, understanding the interplay of nutritional factors with genetic and epigenetic pathways is crucial. Nutrigenomics provides an exciting opportunity to study these interactions and develop precision nutritional strategies that can improve maternal-fetal health outcomes within the unique sociocultural and biological context of Sub-Saharan Africa.

## ➢ *The Rise of Nutrigenomics*

- *What is Nutrigenomics and Nutrigenetics?*

The fast development of the genomic sciences has changed the way nutrition is understood, from a population-based approach to an approach that increasingly takes into account individual biological variability. This change has led to the development of the fields of nutrigenomics and nutrigenetics which together seek to explain the complex interactions between diet and the human genome. Nutrigenomics studies how nutrients, dietary patterns and bioactive food compounds interact with gene expression, signalling pathways, protein synthesis and metabolic processes. In contrast, nutrigenetics is concerned with the effects of genetic differences, especially SNPs (single nucleotide polymorphisms), on individual responses to nutrients and dietary interventions [4].

This is an important distinction between the two disciplines. Nutrigenomics is the study of the effect of diet on gene activity and nutrigenetics is the study of the effect of gene variation on nutrient metabolism and dietary requirements. These fields together form the scientific basis of precision nutrition, which aims to provide personalized dietary recommendations on the basis of the genetic, metabolic, environmental and lifestyle characteristics of an individual [4,5].

Advances in high-throughput sequencing technologies, transcriptomics, proteomics, metabolomics and bioinformatics have allowed the emergence of nutrigenomics. With these technologies, researchers can study the molecular pathways by which nutrients regulate gene expression and impact health outcomes. Recent data suggest that nutritional factors can control the expression of genes involved in inflammation, immune regulation, oxidative stress, lipid metabolism, glucose homeostasis and

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

fetal development, thus nutrition is a potential modifiable determinant of health throughout the life course [5,6].

- *Gene–Nutrient Interactions in Fetal and Maternal Development*

Pregnancy is one of the most important periods during which gene–nutrient interactions affect health outcomes. Maternal nutrition affects fetal growth and development and the regulation of gene expression patterns that can affect susceptibility to disease throughout life. Evidence from both human and animal studies is increasing that maternal dietary exposures during pregnancy can alter fetal development through epigenetic mechanisms such as DNA methylation, histone modification and non-coding RNA regulation [7,8].

The concept of fetal programming, a fundamental basis of the Developmental Origins of Health and Disease (DOHaD) hypothesis, suggests that environmental exposures during critical windows of development can cause lasting biological effects. The maternal nutritional status is one of the most important environmental factors influencing fetal programming. Nutrient deficiencies or excesses during pregnancy may change gene expression in the placenta and fetus, potentially increasing the risk of adverse outcomes, such as low birth weight, preterm birth, neural tube defects, metabolic disorders, cardiovascular diseases, and obesity later in life [7,8].

One of the most studied examples of gene-nutrient interactions in pregnancy is folate metabolism. Polymorphisms of the methylenetetrahydrofolate reductase (MTHFR) gene influence folate use and homocysteine metabolism. Women carrying certain MTHFR polymorphisms may need higher intake of folate and are at higher risk of neural tube defects in the absence of adequate folate intake before and during pregnancy. Likewise, genetic variants affecting vitamin D receptors, iron metabolism, and zinc transport proteins have been associated with changes in pregnancy outcomes and fetal growth patterns [4,7].

Recent studies have further highlighted placenta as a significant mediator of maternal–fetal gene–nutrient interactions. The placenta, an organ of nutrient transport, is also an epigenetically active tissue that is responsive to maternal dietary signals. Nutrients, metabolites from the gut microbiota and maternal metabolic status can alter placental gene expression and epigenetic regulation, thereby affecting fetal growth trajectories and developmental outcomes [8]. These results highlight the importance of understanding the nutrigenomic mechanisms in maternal and child health interventions, especially in regions such as Sub-Saharan Africa where nutritional deficiencies are still highly prevalent.

- *Global Progress in Precision Nutrition*

Precision nutrition as a main paradigm in contemporary nutritional science has been accelerated by the integration of nutrigenomics, nutrigenetics, metabolomics, microbiomics and artificial intelligence. Precision nutrition aims to address the one-size-fits-all dietary recommendations by considering interindividual differences in genetics, metabolism, composition of gut microbiota, lifestyle, and environmental exposures [5,9].

Several large-scale initiatives have been instrumental in advancing precision nutrition research globally. Studies using genomic sequencing, metabolomic profiling and microbiome analyses have demonstrated considerable variability in individual responses to the same dietary interventions. These findings have challenged the classical “one-size-fits-all” approach to nutrition and have emphasized the need for more personalized dietary strategies [9,10].

Recent advances in multi-omics technologies have improved the detection of biological markers related to nutrient responses. By integrating genomic, transcriptomic, proteomic, metabolomic and microbiome data, researchers are better able to characterize the complex biological networks underlying nutrition-related health outcomes. Such approaches are increasingly adopted in the prevention and management of obesity, diabetes, cardiovascular diseases and maternal health conditions [10].

Emerging as powerful tools for precision nutrition are also artificial intelligence and machine learning. Sophisticated computational models can integrate large biological and clinical data sets to predict individual responses to dietary interventions and to support personalized nutrition guidance. These new inventions are expected to improve dietary planning, disease prevention, and health care delivery, as well as stimulate more effective public health strategies [9,11].

However, large disparities remain in the global distribution of nutrigenomics research. Most genomic databases and studies of precision nutrition have been conducted in high-income countries, leading to underrepresentation of African populations. This lack of knowledge limits the transferability of existing evidence to different genetic backgrounds and dietary settings in Sub-Saharan Africa. There is thus a need to increase nutrigenomics research in African populations in order to develop culturally specific and genetically based nutritional interventions that will improve the health of mothers and their babies in Africa.

➢ *The Reason to Undertake the Review*

- *Nutrigenomics Evidence is Scarce in Sub-Saharan Africa*

Nutrigenomics is an area that has grown enormously in the last 20 years. This emergence has led to important discoveries about the interactions between dietary factors and genetic and epigenetic mechanisms affecting health and disease. Despite these advances, the vast majority of nutrigenomic research has been carried out in North America, Europe and parts of Asia, with African populations still being significantly under-represented in genomic and nutrition research [14,16]. This discrepancy is a major challenge as the genetic diversity among the African populations is higher than the other population groups in the world, which means that findings in non-African populations may not be translatable to Sub-Saharan African populations directly [16].

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

The underrepresentation of African populations in genomic databases and precision nutrition studies has resulted in important knowledge gaps in gene-nutrient interactions pertinent to maternal and fetal health [14]. Many genetic variants linked to nutrient metabolism, micronutrient utilization, inflammatory responses, and disease susceptibility have been identified mainly in populations of European ancestry [14]. This constrains the development of evidence-based nutritional interventions specific to the local genetic make-up because the biological mechanisms underlying maternal nutritional responses in African women are poorly understood.

Omics technologies, such as genomics, epigenomics, metabolomics and proteomics, are being used more and more around the world, but are under-utilised in maternal health research in Sub-Saharan Africa. A systematic review of pregnancy cohorts and biobanking initiatives in sub-Saharan Africa identified relatively few cohorts with biological sample repositories available for genomic and nutrigenomic investigations [12]. Moreover, these cohorts were limited to a few countries, such as South Africa, Tanzania, Mozambique and Benin, with numerous regions poorly or not being represented [12].

Similar findings have been documented from mapping studies that revealed large gaps in maternal health research priorities in Sub-Saharan Africa [13]. Although the number of studies involving nutrition has increased, the number of studies using genomic, epigenetic or precision nutrition approaches remains relatively low [13]. The majority of existing studies have focused on traditional nutritional interventions, dietary assessments and public health outcomes, rather than the molecular pathways of nutrients in maternal and fetal development.

The lack of nutrigenomic evidence is particularly worrying given the region's disproportionate burden of maternal mortality, low birth weight, preterm birth, childhood stunting, and micronutrient deficiencies [15]. Without robust nutrigenomic evidence from African populations, opportunities for identifying high-risk groups, optimizing nutritional interventions, and improving maternal and fetal outcomes may remain unfulfilled.

- *The Need for Policies on Maternal Nutrition in Context*

In most Sub-Saharan African countries, maternal nutrition policies are largely informed by global recommendations based on evidence produced from outside the African context [14]. While these guidelines have contributed to improvements in maternal and child health, they often assume more or less uniform nutritional responses across populations. These guidelines may not adequately take into account the genetic, cultural, environmental and dietary heterogeneity observed within African contexts.

The wide-ranging maternal nutritional challenges across the region further reinforces the importance of context-specific maternal nutrition policies. Food insecurity, ongoing infectious diseases, climate-related shocks, cultural food taboos, low dietary diversity and poor access to antenatal nutrition services continue to affect maternal dietary patterns and pregnancy outcomes [17]. There is recent evidence that food taboos and dietary restrictions in pregnancy are common in Sub-Saharan Africa and are associated with nutritional deficiencies and adverse maternal-fetal outcomes [17].

Emerging evidence from developmental programming and epigenetic research suggests that maternal nutritional exposures during pregnancy can affect fetal gene expression and subsequent health trajectories [14]. These findings suggest that maternal nutrition policies should move beyond generalized supplementation strategies toward more targeted interventions that consider population-specific nutritional risks, genetic variability, and environmental exposures.

Moreover, the increasing availability of genomic technologies, biobanking infrastructure and multi-omics research platforms in Africa provides a unique opportunity to integrate nutrigenomics into maternal and child health programs [12,16]. Building up local research capacity and generating African-specific evidence could lead to development of culturally-appropriate, genetically-informed maternal nutrition guidelines that can address the region's specific health problems. Thus, a timely and necessary comprehensive review of the current evidence on gene-nutrient interactions in maternal-fetal health to inform future research priorities, policy development and precision nutrition strategies across Sub-Saharan Africa.

➢ *The Aim of the Review*

The rising burden of maternal and fetal health challenges in Sub-Saharan Africa coupled with the growing recognition of gene–nutrient interactions as key determinants of pregnancy outcomes highlight the need for a comprehensive synthesis of available evidence within this nascent field. Nutrigenomics has provided considerable knowledge about the molecular mechanisms that explain the effects of nutrition on health and disease, but evidence in African populations remains fragmented and limited. This has led to a lack of understanding of how genetic variation, nutritional exposures and environmental factors interact to influence maternal and fetal health outcomes in the diverse populations of Sub-Saharan Africa.

Maternal nutrition is a major determinant of fetal growth, pregnancy outcomes and long-term health of offspring. Recent evidence suggests that genetic polymorphisms, epigenetic modifications and nutrient-sensitive molecular pathways may be critical in the risk of micronutrient deficiencies, pregnancy complications, fetal growth restriction and developmental disorders. However, most current evidence is derived from high-income countries, where the genetic backgrounds, dietary patterns, healthcare systems and environmental exposures are considerably different from those in Sub-Saharan Africa. These differences underscore the importance of critically assessing the relevance of the current knowledge base in nutrigenomics for African populations and setting context-specific research priorities.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

Moreover, while investments in genomic research are increasing in Africa, significant barriers remain to advance research in nutrigenomics and its integration in maternal and child health programs. The limited laboratory infrastructure, lack of funding, absence of genomic databases, lack of skilled personnel, ethical concerns, and weak policy frameworks have hampered the generation and translation of evidence into practice. Understanding these barriers is important to inform future research agenda and to strengthen the implementation of precision nutrition strategies in the region. The present review aims to compile the current knowledge on the role of gene-nutrient interactions in maternal-fetal health in this context, and to evaluate their relevance to Sub-Saharan Africa. In particular, the review is guided by the following objectives:

- *General Objective*

To critically review current evidence on gene-nutrient interactions and their implications for maternal-fetal health in Sub-Saharan Africa, with the goal of informing future research, policy development and precision nutrition interventions.

- *Objectives*

✓ To review the present evidence on gene-nutrient interactions impacting maternal-fetal health.
✓ To determine the challenges that are limiting nutrigenomics research in sub-Saharan Africa.
✓ To discuss policy implications and future perspectives of maternal-fetal nutrigenomics in Sub-Saharan Africa.

- *Research Questions*

✓ What is the evidence for gene–nutrient interactions on maternal and fetal health outcomes in Sub-Saharan Africa?
✓ What genetic variants and nutritional factors have been most often associated with maternal and fetal health outcomes?
✓ Barriers to the development and implementation of nutrigenomics research in Sub-Saharan Africa
✓ What is the potential of nutrigenomics evidence to inform maternal nutrition policies and precision health strategies in the region?
✓ What are future research priorities to advance maternal-fetal nutrigenomics in African populations?

## II. METHOD OF STUDY

A narrative review (document review) design was used to synthesize and critically evaluate the current evidence on gene-nutrient interactions and their implications for maternal-fetal health in Sub-Saharan Africa. The narrative review approach was chosen because nutrigenomics is an emerging and multidisciplinary field characterized by heterogeneous study designs and outcome measures. The review focused on peer-reviewed articles, systematic reviews, policy documents, technical reports, and scholarly publications relevant to maternal nutrition, nutrigenomics, nutrigenetics, epigenetics, fetal development, and precision nutrition.

A comprehensive literature search was performed from May to June 2026 using PubMed/ MEDLINE, Scopus, Web of Science and Google Scholar. Additional sources were identified through manual searches of reference lists and reports of international organizations. The search terms included combinations of keywords such as nutrigenomics, nutrigenetics, gene-nutrient interactions, maternal nutrition, pregnancy, epigenetics, fetal development, precision nutrition, and Sub-Saharan Africa. The search was restricted to English language publications from January 2010 to June 2026 to capture the most recent developments in maternal-fetal nutrigenomics research.

Studies were eligible if they studied gene-nutrient interactions, nutrigenomics, nutrigenetics, epigenetics or precision nutrition in relation to maternal, fetal, neonatal or child health. results. Eligible publications were original research articles, systematic reviews, meta-analyses, cohort studies, randomized controlled trials and policy reports. Extracted data from eligible studies were study characteristics, nutrients investigated, genetic or epigenetic factors assessed, health outcomes, and key findings. The evidence was thematically synthesized on biological mechanisms of gene–nutrient interactions, maternal nutrition and fetal programming, current nutrigenomics evidence in Sub-Saharan Africa, research gaps, implementation challenges, and policy implications for precision nutrition.

## III. FRAMEWORK OF CONCEPTS

➢ *Maternal Nutrition and Fetal Programming*

- *Developmental Origins of Health and Disease (DOHaD)*

The best way to understand the association between maternal nutrition and fetal health is the Developmental Origins of Health and Disease (DOHaD) framework. The DOHaD hypothesis proposes that environmental factors in critical developmental periods, especially around conception, pregnancy, and early infancy, can exert profound and long-lasting effects on physiological function, disease susceptibility and health throughout the lifespan [18]. Among environmental influences, maternal nutrition has been identified as one of the most critical determinants of fetal growth, developmental programming, and future health.

The idea stems from the seminal work of epidemiologist David Barker who identified links between low birth weight and increased risk of cardiovascular disease, hypertension and type 2 diabetes in adulthood. From these observations, the “Barker Hypothesis” was born, which then developed into the larger DOHaD framework. According to the theory, poor nutritional conditions in the womb can cause permanent structural, physiological and metabolic adaptations that might enhance short-term survival but increase susceptibility to chronic diseases later in life [19].

The DOHaD model proposes that fetal development is marked by higher biological plasticity that allows adaptation to environmental signals from the mother. Maternal nutritional status is a major source of such signals. Nutritional deficits or excesses during pregnancy can affect the

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

development of fetal organs, endocrine function, metabolic pathways and gene expression patterns. These adaptations can modify fetal growth trajectories and set physiological traits that remain into adulthood [20].

Maternal undernutrition remains one of the major public health problems in many parts of sub-Saharan Africa. Deficiencies in key nutrients such as iron, folate, iodine, zinc, calcium, vitamin D and protein can impact placenta development, decrease the transfer of nutrients to the foetus and lead to adverse pregnancy outcomes such as low birth weight, intra-uterine growth restriction, pre-term birth and neo-natal mortality [21]. On the other hand, too much maternal energy intake and obesity may predispose offspring to metabolic disorders through altered fetal programming mechanisms. Maternal nutritional status at both extremes can interfere with normal developmental processes and influence the risk of disease throughout life [22].

Fetal programming is a core concept of the DOHaD framework. Fetal programming is defined as the process by which environmental stimuli during critical periods of development result in long-term changes in the structure and function of tissues, organs and biological systems [13]. Nutritional exposures during pregnancy are among the most potent programming factors because they influence critical developmental processes such as cell proliferation, differentiation, angiogenesis and organogenesis [23].

There is increasing evidence that the programming of the fetus is largely mediated by epigenetic mechanisms. Epigenetics is the study of heritable phenotype changes that do not involve changes in the DNA sequence. The main epigenetic mechanisms include DNA methylation, histone modification and regulation by non-coding RNAs. These epigenetic processes are directly influenced by substrates and cofactors in the maternal diet. For example, the pathways of DNA methylation that regulate gene expression during fetal development involve folate, vitamin B12, choline, methionine and other one-carbon metabolism nutrients [24].

Research has shown that nutritional imbalances during pregnancy can lead to epigenetic modifications in genes associated with metabolism, immune response, neurodevelopment and cardiovascular regulation. These changes may persist throughout life and influence susceptibility to obesity, diabetes mellitus, hypertension, cardiovascular disease, and other non-communicable diseases [25]. These findings have reinforced the biological plausibility of the DOHaD hypothesis and highlighted the importance of maternal nutrition in shaping population health.

The placenta is pivotal to the DOHaD paradigm because it is the tissue that mediates communication between the maternal and fetal environments. Traditionally the placenta has been viewed as an organ for nutrient transport, but it also functions as an endocrine and epigenetic regulator that can respond to maternal dietary cues. The maternal supply of nutrients can influence placental gene expression, efficiency of nutrient transport, inflammatory pathways, and fetal growth patterns. Thus, placental adaptations can magnify or diminish the impact of maternal nutrient exposures on fetal development [26].

Recent developments in the field of nutrigenomics have extended the DOHaD framework by demonstrating the role of individual genetic variation in the response to maternal nutritional exposures. Gene–nutrient interactions may affect the metabolism, transport, and utilization of nutrients in pregnancy. For example, alterations in genes involved in folate metabolism, iron homeostasis, vitamin D signaling, and lipid metabolism may influence pregnancy outcome and fetal development. These results suggest that the nutritional status as well as the nutrient-maternal fetal genome interactions [27] influence maternal fetal health outcomes.

The DOHaD framework is especially pertinent in Sub-Saharan Africa where many populations are burdened by chronic maternal undernutrition, micronutrient deficiencies, infectious diseases, food insecurity and limited access to healthcare . These exposures may contribute to adverse fetal programming and increase the risk of poor health outcomes across generations . Thus, understanding the interactions between maternal nutrition, genetic factors, epigenetic regulation and fetal development is essential to develop effective maternal nutrition interventions and precision health strategies tailored for African populations.

The DOHaD concept is the conceptual framework for this review that demonstrates how maternal nutritional exposures interact with genetic and epigenetic mechanisms to influence fetal development and health outcomes throughout life. It also supports the rising interest in nutrigenomics as a tool to enhance maternal-fetal health with evidence-based and context-specific nutrition interventions.

➢ *Interactions Between Genes and Nutrients*

Gene–nutrient interactions are the basic biological processes through which dietary components influence gene activity and, on the other hand, genetic variation influences nutrient metabolism, utilization, and physiological responses. These interactions are the basis of nutrigenomics and nutrigenetics, and are increasingly recognized as important determinants of maternal and fetal health outcomes. Nutrients in pregnancy are substrates for fetal growth and development, and also signaling molecules that can regulate gene expression, cellular differentiation, placental function, and metabolic programming [28]. Therefore, knowledge of the molecular mechanisms underlying gene–nutrient interactions is essential for understanding variability in pregnancy outcomes and for developing precision nutrition strategies for maternal and child health.

- *Mechanisms of Regulation of Gene Expression*

Gene expression is the process by which information encoded in DNA is translated into products such as proteins or regulatory molecules. The regulation of gene expression is a highly coordinated process that controls the timing, place, and magnitude of gene activation or repression. Nutrients impact this process at multiple levels, influencing cellular function and developmental outcomes [29].

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

At the molecular level, nutrients can act as signaling molecules that interact with transcription factors, nuclear receptors and intracellular signaling pathways. These interactions control the transcription of particular genes involved in growth, metabolism, immune function, inflammation, and development. Vitamins, minerals, fatty acids, amino acids, and phytochemicals have all been shown to affect gene expression via such mechanisms [30].

The fundamental process of gene expression is transcription, in which DNA is transcribed into messenger RNA (mRNA).

Nutritional factors can also directly affect transcriptional activity by altering the availability of transcription factors and co-factors required for gene activation. For example, vitamin D binds to the vitamin D receptor (VDR) which then forms a complex that controls the expression of many genes involved in calcium homeostasis, immune responses and placental development. Similar to this, omega-3 fatty acids may activate peroxisome proliferator-activated receptors (PPARs), which control genes involved in lipid metabolism and inflammation [31].

After transcription, messenger RNA is translated into proteins, which are responsible for the structure and function of the cell.

Nutritional status of the mother can affect transcriptional and translational processes. Essential nutrient deficiencies can interfere with protein synthesis, alter enzyme function and disrupt developmental pathways critical to fetal growth. Conversely, adequate nutrient availability supports optimal cellular differentiation, tissue formation and organ development during gestation [32].

Genetic polymorphisms also explain variations in individual responses to nutrients. Single nucleotide polymorphisms (SNPs) in genes involved in nutrient metabolism may affect nutrient requirements and enzyme function. A well-studied example is the methylenetetrahydrofolate reductase (MTHFR) gene. Variants of the MTHFR gene impair folate metabolism and increase the risk of elevated homocysteine, neural tube defects, recurrent pregnancy loss and adverse pregnancy outcomes when folate intake is inadequate [33]. Comparable associations have been reported for genes involved in iron metabolism, vitamin D signaling, zinc transport and lipid metabolism, emphasizing the complex interplay between genetic variation and nutritional exposures during pregnancy.

- *Pregnancy Outcomes and Epigenetics*

Epigenetics is one of the most important mechanisms by which maternal nutrition relates to fetal development and long-term health outcomes. Epigenetics is the study of heritable changes in gene expression that do not involve changes to the underlying DNA sequence. These changes are involved in the regulation of gene activity and are sensitive to environmental factors, particularly during critical periods of development, such as the diet during pregnancy [34].

Three major epigenetic mechanisms were identified:

- ✓ DNA methylation
- ✓ Modification of histone
- ✓ Non-coding RNA regulation

Among these, DNA methylation is the most investigated mechanism in maternal-fetal nutrigenomics. DNA methylation is the process of adding methyl groups to particular parts of DNA, which can turn genes off or on. Nutrients involved in one-carbon metabolism, such as Folate, vitamin B12, choline, methionine and betaine provide the methyl donors required for this process. Hence, maternal diet has a direct effect on fetal epigenetic programming [35].

Epigenetic modifications during pregnancy are crucial for placental development, fetal growth, organogenesis and immune maturation. Maternal nutritional deficiencies can disturb normal epigenetic regulation, resulting in altered gene expression patterns that may last a lifetime. These changes have been associated with low birth weight, neurodevelopmental impairment, metabolic disorders, obesity, type 2 diabetes, cardiovascular disease and immune dysfunction [36].

There is a considerable body of evidence from the Developmental Origins of Health and Disease (DOHaD) concept supporting the role of epigenetic programming in pregnancy outcomes. For example, studies based on historical famine events, such as the Dutch Hunger Winter, demonstrated that maternal undernutrition during pregnancy led to permanent DNA methylation changes in offspring, which increased the risk for chronic diseases decades later [37]. These findings then provided a biological framework to understand the influence of maternal nutrition on lifelong health trajectories.

Emerging data also suggest that maternal overnutrition and obesity may cause epigenetic changes affecting the metabolic health of the offspring . Increased energy intake by the mother, gestational diabetes and obesity have been linked with changes in genes involved in insulin signaling, adipogenesis, inflammation and appetite control. These changes may predispose the offspring to obesity and metabolic disorders later in life [38].

The placenta is a major mediator of nutritional and epigenetic influences during pregnancy. Maternal diet exposures can change placental gene expression, nutrient transport systems, inflammatory pathways and epigenetic profiles. These adaptations of the placenta affect fetal nutrient availability and developmental programming and thus birth outcomes and risk of disease later in life [39].

Epigenetic mechanisms might be important for adverse maternal and fetal outcomes in Sub-Saharan Africa, where maternal undernutrition, micronutrient deficiencies, food insecurity and infectious diseases remain prevalent. But evidence from African populations is limited, suggesting that more research is needed to understand population-specific gene–nutrient interactions and epigenetic responses. Such

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

research expansion could underpin the development of targeted nutritional interventions to improve pregnancy outcomes and reduce the intergenerational burden of disease across the region.

Gene–nutrient interactions and epigenetic regulation provide the biological foundation for the effects of maternal nutrition on fetal development and lifelong health . These mechanisms help explain the individual variability in nutritional responses and offer promising opportunities for precision nutrition approaches designed to optimize maternal-fetal health outcomes.

- *Precision Nutrition in Pregnancy*

Precision nutrition is a new paradigm in nutritional science that seeks to improve health outcomes by personalizing dietary advice based on a person's genes, metabolism, environmental exposures, lifestyle and physiology. Different from traditional nutrition approaches that rely on general dietary recommendations for entire populations, precision nutrition takes into account large inter-individual variations in nutritional needs and responses to dietary interventions. This paradigm shift has very profound implications for maternal health where the nutritional needs are very dynamic and do directly influence both maternal well-being and fetal development [40].

Pregnancy is associated with profound physiological, hormonal and metabolic changes that increase the demands and modify the utilization of nutrients. Good nutrition during this time is necessary to help the growth of the placenta, to support the growing foetus, to allow the tissues of the mother to expand and to keep the mother healthy. Nevertheless, nutritional status and responses to supplementation are often significantly heterogeneous among women due to differences in genetic makeup, epigenetic profiles, metabolic function, gut microbiota composition, socioeconomic circumstances, and environmental exposures [41]. Precision nutrition tries to take these differences into account and to customize specific nutritional interventions which would give the maximum benefits and minimum adverse outcomes.

Advances in nutrigenomics and nutrigenetics are closely related to the scientific basis of precision nutrition. Nutrigenomics researches the influence of nutrients on gene expression . Nutrigenetics researches the effect of genetic variations on the metabolism of nutrients and responses to diet . Together, these disciplines can offer some insight into why people might respond differently to the same nutritional intervention. This knowledge is particularly relevant during pregnancy, where gene-nutrient interactions can influence maternal health, placental function, fetal growth and the long-term health of the offspring [42].

Folate metabolism is one of the most studied examples of precision nutrition in maternal health. Adequate folate intake before conception and early pregnancy is critical to prevent neural tube defects and support fetal development. However, genetic variations in the methylenetetrahydrofolate reductase (MTHFR) gene can affect folate metabolism and increase folate requirements. Standardized folate recommendations may not be optimal for all women and individualized folate supplementation strategies may benefit women with certain MTHFR polymorphisms. This example suggests the potential of genetic information to inform more effective maternal nutrition interventions [43].

Precision nutrition approaches have also been explored for iron metabolism in pregnancy. The requirement for iron rises substantially to meet the needs of the expanding maternal blood volume and fetal growth. Genetic variation in genes involved in iron absorption, transport and storage may however influence susceptibility to iron deficiency anemia and response to supplementation. Personalized approaches to iron supplementation based on genetic and biochemical evaluation may improve maternal outcomes while reducing risks for inappropriate supplementation [44].

Another example of the importance of precision nutrition in pregnancy is vitamin D metabolism. Genetic variants influencing vitamin D receptors and enzymes involved in vitamin D activation may affect maternal vitamin D levels and biological responses. Such variations may contribute to differences in pregnancy outcomes, including risks of preeclampsia, gestational diabetes, and impaired fetal skeletal development. Precision nutrition approaches could therefore help identify women who need increased vitamin D monitoring and supplementation in pregnancy [45].

The emergence of multi-omics technologies has expanded the field of precision nutrition beyond the scope of single nutrients. Genomics, epigenomics, transcriptomics, proteomics, metabolomics and microbiomics now provide holistic views of biological mechanisms of nutritional responses. These technologies allow researchers to identify biomarkers associated with nutritional status, disease risk, and intervention effectiveness. In maternal health, multi-omics approaches are increasingly being used to investigate pregnancy complications, fetal growth patterns, placental function, and developmental programming processes [46].

Another key element of precision nutrition that has emerged is the maternal gut microbiome. The gut microbial communities affect nutrient absorption, immune regulation, inflammation and metabolic function. Dietary interventions may modify the gut microbiota that can influence maternal health and fetal development and the gut microbiota is altered by pregnancy. Microbiome analyses integrated into maternal nutrition programming could improve understanding of individual responses to nutrition and enable more targeted interventions [47].

Recent advances in artificial intelligence (AI), machine learning and digital health technologies are accelerating the development of precision nutrition. These technologies can combine large-scale genomic, clinical, dietary and environmental data to generate personalised nutrition recommendations. AI-based predictive models have shown promise for the identification of women at risk of negative pregnancy outcomes and for the personalization of nutritional interventions. Such innovations may improve antenatal care

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

through early risk identification and evidence-based nutritional decision-making [48].

However, there are a number of challenges in implementing precision nutrition in maternal health despite its promise. Genetic testing, omics technologies and personalised nutrition services remain expensive and are not available in many low- and middle-income countries. Translation of precision nutrition to routine healthcare practice is limited by inadequate genomic infrastructure, funding, technical expertise, and underrepresentation of African populations in genomic research databases. Moreover, ethical issues regarding genetic privacy, informed consent, data ownership and equitable access need to be carefully considered to ensure responsible implementation [49].

In Sub-Saharan Africa, where maternal undernutrition, micronutrient deficiencies, food insecurity and adverse pregnancy outcomes continue to be pervasive, precision nutrition presents a potentially useful framework to improve maternal-fetal health. The region has significant genetic diversity, which can affect nutrient requirements and responses to interventions. However, the limited amount of nutrigenomic research in African populations limits the current understanding of these relationships. Developing culturally appropriate and genetically informed maternal nutrition policies will require expanding research capacity, strengthening genomic infrastructure and generating population-specific evidence [50]. Precision nutrition is, in the end, an evolution from generalized nutritional recommendations to context-specific, individualized dietary interventions. Precision nutrition that integrates genomic data, nutritional science, epigenetics and digital health innovations could enhance maternal health outcomes, optimize fetal development and aid in the prevention of infectious and non-infectious diseases across generations. With evidence for nutrigenomics mounting, precision nutrition may be an increasingly important component of maternal and child health strategies in Sub-Saharan Africa and beyond.

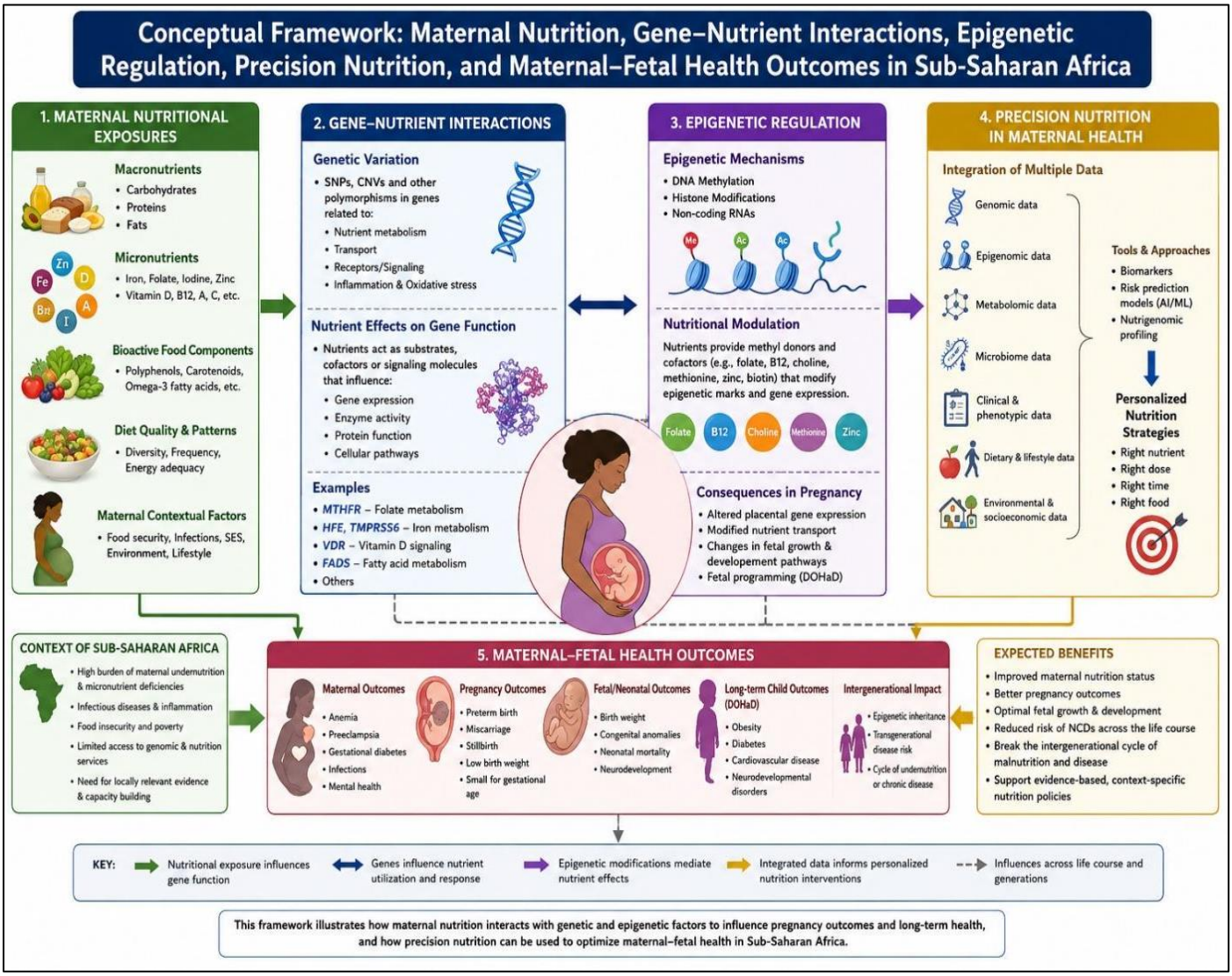


Fig 1 Conceptual Framework: Maternal Nutrition. Gene Nutrient Interaction, Epigenetic Regulation, Precision Nutrition, and Maternal Fetal Health Outcomes in Sub-Sahara Africa Authors' conceptualization based on Barker (1995), Gluckman et al. (2010), Ferguson et al. (2016), Ordovas et al. (2018) and Basak et al. (2024).

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

## IV. CURRENT EVIDENCE OF GENE-NUTRIENT INTERACTIONS IN MATERNAL-FETAL HEALTH

### *A. Folate Metabolism and MTHFR-Variants*

➢ *Folate Metabolism and its Significance in Pregnancy*

Folate (vitamin B9) is one of the most important micronutrient during pregnancy, and plays an essential role in DNA synthesis, nucleotide biosynthesis, cellular proliferation, amino acid metabolism and methylation reactions. Folate is needed in greater amounts during pregnancy to help support the rapid growth of maternal tissue, the development of the placenta and the division of fetal cells . Adequate folate availability is especially important in the early phases of embryogenesis when the neural tube is formed between the third and fourth weeks after conception [51].

Folate is involved in one-carbon metabolism, a biochemical pathway that mediates transfer of methyl groups necessary for DNA synthesis and epigenetic regulation. In this pathway, the enzyme methylenetetrahydrofolate reductase (MTHFR) catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the biologically active form of folate involved in the remethylation of homocysteine to methionine [52]. Methionine then acts as a precursor for S-adenosylmethionine (SAM), the principal methyl donor for DNA methylation and gene expression control during fetal development.

As folate metabolism is a key player in methylation and cell proliferation, disturbances can have a major impact on embryonic and foetal development. Genetic polymorphisms in the MTHFR gene have been one of the most extensively studied examples of gene-nutrient interactions affecting maternal-fetal health.

➢ *Folate Metabolism and MTHFR Gene Variants*

The MTHFR gene is located on chromosome 1p36.22 and encodes the MTHFR enzyme that regulates folate metabolism and homocysteine homeostasis. Two polymorphisms have been extensively studied:

- C677T (rs1801133)
- A1298C (rs1801133)

Particularly the C677T variant is the most studied variant. The homozygous TT genotype is linked with a marked decrease in MTHFR enzymatic activity, with individuals maintaining only 25-35% of normal activity. Decreased enzyme activity results in decreased production of active folate and increases plasma homocysteine concentrations, especially in the case of suboptimal dietary folate intake [53].

Hyperhomocysteinemia has been linked to endothelial dysfunction, oxidative stress, impaired placental vascularization and abnormal fetal development. This means the women with MTHFR polymorphisms may be more susceptible to adverse pregnancy outcomes, particularly in populations with insufficient folate intake [54].

The frequency of MTHFR variants varies widely among populations. Extensive data exist for populations from Europe, Asia and North America but there is relatively less evidence for Sub-Saharan African populations. However, the available studies suggest a high degree of genetic variability in African populations, stressing the need of region-specific studies on folate-related genetic risk factors [55].

➢ *Neural Tube Defect*

Neural tube defects (NTDs) are the most studied adverse outcome associated with altered folate metabolism and MTHFR polymorphisms. NTDs are severe congenital malformations caused by failure of neural tube closure during early embryogenesis. Typical forms are:

- Spina bifida
- Anencephalus
- Encephalocele.

NTDs remain a major cause of neonatal mortality, disability, and long-term neurological impairment worldwide [56].

Several epidemiological studies and meta-analyses have shown associations between maternal MTHFR C677T polymorphisms and increased risk of NTDs. Women with the TT genotype are generally at a significantly higher risk of having pregnancies affected by NTDs, especially when the intake of folate is low. It is thought that the mechanism is related to decreased methylation capacity, impaired DNA synthesis, and altered embryonic cell proliferation during the process of neural tube formation [57].

There is also evidence that maternal folate deficiency and MTHFR variants may act in a synergistic manner. Genetic predisposition does not inevitably result in NTDs. Often the adverse outcome arises when genetic risk is combined with inadequate folate availability. This interaction is the paradigm of the main principle of nutrigenomics where nutritional exposures modify the effects of genetic variation on health outcomes [58].

The wide-scale fortification of staple foods with folic acid has been successful in reducing the incidence of NTDs in many countries, providing evidence that folate is biologically important in early pregnancy. However, folic acid fortification coverage and implementation are still inconsistent in many Sub-Saharan African countries which could contribute to the ongoing preventable NTD cases [59].

➢ *MTHFR Variants Pregnancy Complications*

In addition to neural tube defects, MTHFR polymorphisms have been linked to several adverse pregnancy outcomes. Disturbed folate metabolism may lead to increased homocysteine levels which can interfere with placental function and uteroplacental circulation, rendering it vulnerable to pregnancy complications [60].

➢ *Recurrent Pregnancy Loss (RPL)*

MTHFR variants have been reported in several studies to be associated with recurrent pregnancy loss. Impaired

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

folate metabolism and hyperhomocysteinemia might contribute to placental thrombosis, endothelial dysfunction and impaired implantation and increase the risk of miscarriage. Despite some inconsistency in results between populations, many systematic reviews do support a modest association between MTHFR polymorphisms and recurrent pregnancy loss, particularly when combined with low folate status [61].

➢ *Preeclampsia*

Preeclampsia is a hypertensive disorder defined by maternal hypertension and organ dysfunction after 20 weeks of gestation. There is increasing evidence to suggest a role for MTHFR associated hyperhomocysteinemia in endothelial damage, oxidative stress and abnormal placentation, increasing the risk for preeclampsia. Meta-analysis studies have shown that the rate of MTHFR C677T variants is higher in women with preeclampsia than in normal controls [62].

➢ *Preterm Birth and Low Birthweight*

Defective folate metabolism has also been associated with increased risks of preterm birth and low birth weight. Lower folate availability may influence placental vascular development, nutrient transport and fetal growth. High homocysteine levels have been associated with placental insufficiency and poor fetal growth that are linked to poor neonatal outcomes [63].

➢ *Disorders of the Placenta*

Indeed, several studies have associated MTHFR variants with placental abruption, intrauterine growth restriction, and other placental dysfunction syndromes. These results further emphasize the importance of sufficient folate metabolism for maintaining healthy placental development and fetal growth [64].

➢ *Folic Acid Supplementation and Precision Nutrition Approaches*

Folic acid supplementation has been one of the most successful nutritional interventions in maternal health. International guidelines recommend women of reproductive age to take folic acid before conception and during early pregnancy to reduce the risk of neural tube defects and other folate-related problems [65].

Increasing evidence from nutrigenomics, however, suggests that uniform supplementation strategies may not fully accommodate the individual differences in folate metabolism. Women with MTHFR polymorphisms may have a decreased ability to convert synthetic folic acid into folate that is available to the body. Therefore, some researchers have suggested the use of 5-methyltetrahydrofolate (5-MTHF), the active form of folate, as a different supplementation strategy in genetically susceptible individuals [66].

This personalized approach is in line with the principles of precision nutrition aiming at tailoring nutritional interventions according to genetic and metabolic characteristics . Currently, routine genetic screening for MTHFR variants is not recommended in most clinical settings, but advances in nutrigenomics may eventually allow for more personalized maternal nutrition programs, especially in high-risk populations [67].

*B. Genes Involved in Iron Metabolism and Maternal Anemia*

➢ *Maternal Health and Iron Metabolism*

Iron is an essential micronutrient that is required for many physiological processes such as oxygen transport, cellular respiration, DNA synthesis, immune function and fetal development. Maternal iron requirements are greatly increased during pregnancy because of the expansion in maternal blood volume, erythropoiesis, growth of the placenta and iron requirements of the fetus. Pregnant women are particularly vulnerable to iron deficiency in the setting of low dietary intake and body stores, with the estimated need for an additional 1,000 mg of iron during pregnancy to meet maternal and fetal requirements [68].

Maternal iron deficiency is still one of the most widespread nutritional disorders worldwide, with a disproportionately high prevalence among women in Sub-Saharan Africa. The region has some of the highest rates of maternal anemia globally, with causes including poor dietary iron intake, recurrent infections, malaria, parasitic infestations, frequent pregnancies, and limited access to antenatal nutritional services [69]. According to the World Health Organization, nearly 40% of pregnant women worldwide are affected by anemia, and iron deficiency accounts for approximately half of all cases [70].

Environmental and nutritional factors are the major contributors to iron deficiency, but emerging evidence strongly suggests that genetic factors influence iron absorption, transport, storage and utilization. Therefore, gene–nutrient interactions of genes involved in iron metabolism have become an important aspect of research in maternal-fetal nutrigenomics.

➢ *Genetic Control of Iron Metabolism*

Iron homeostasis is controlled by the concerted action of a number of genes and proteins that regulate iron uptake, transport, storage and recycling in a complex multi-layered process. The main genes related to iron metabolism are:

- HFE (High Iron Fe)
- HAMP (Hepcidin Antimicrobial Peptide)
- Transferrin (TF) (
- TFR2 (Transferrin Receptor 2)
- SLC40A1 (Ferroportin)
- TMPRSS6 (Transmembrane protease serine 6)

These genes are coordinately regulated in order to maintain an optimal iron status in avoiding iron deficiency and iron overload [71].

Iron is mainly regulated by hepcidin, a hormone produced in the liver and encoded by the HAMP gene. The key regulator of systemic iron availability is hepcidin, which regulates the cellular iron exporter ferroportin. During

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

pregnancy, hepcidin concentrations are physiologically suppressed to facilitate increased maternal iron absorption and transfer of iron to the fetus. Genetic variation in hepcidin regulation could thus influence maternal iron status and pregnancy outcomes [72].

Of all the iron metabolism genes, the HFE gene has been most extensively studied in relation to pregnancy and maternal anemia.

➢ *HFE Gene Mutations*

HFE gene is located on chromosome 6p22.2 and encodes a protein that helps the body sense iron and control how much iron is absorbed from the intestine. Mutations in this gene affect iron homeostasis by disrupting the interaction of HFE proteins with transferrin receptors, and thus affect hepcidin signaling pathways [73].

Two HFE polymorphisms have been extensively studied:

- C282Y (rs1800562)
- rs1799945 (H63D)

The most common association of these variants is with hereditary hemochromatosis, a condition of excess iron absorption and iron overload. However, their effects on maternal iron status are more complex and may vary with nutritional status, ethnicity and physiological demands during pregnancy [74].

Women with HFE variants may have different efficiency of iron absorption compared to non-carriers. Some evidence suggests that heterozygous carriers may be partially protected from iron deficiency because of increased iron absorption and retention. A hypothesis has been proposed by researchers based on this observation that some HFE variants may have been selected for in populations exposed to iron-deficient environments in the past [75].

However, data on the effect of HFE variants in pregnancy are still inconclusive. Some studies show better iron stores in carriers but others report possible associations with oxidative stress, pregnancy complications and abnormal placental function. These differences may be attributed to population genetics, nutritional environments and study methodologies [76].

There is little data on HFE polymorphisms in African populations. The classical HFE mutations are generally less common in African populations compared to European populations where C282Y mutations are relatively common but other iron-related genetic variants that influence iron metabolism may be present. This underscores the necessity for population-specific studies exploring the genetic determinants of maternal anemia in Sub-Saharan Africa [77].

➢ *Iron Deficiency and Fetal Growth*

Iron deficiency during pregnancy has serious adverse effects on both maternal and fetal health. As iron is required for oxygen transport and cellular metabolism, poor maternal iron stores can impair placental function and reduce oxygen delivery to developing fetal tissues [78].

Many adverse pregnancy outcomes including: iron deficiency anemia in mothers has been associated with.

- Low birth weight
- Preterm delivery
- Intrauterine growth retardation
- Small for gestational age infants
- Perinatal mortality increased
- Modified neurodevelopment

There are several biological mechanisms by which maternal iron status is related to fetal growth.

Firstly, maternal anemia decreases hemoglobin levels and oxygen carrying capacity, thus limiting oxygen supply to the placenta and fetus. Chronic fetal hypoxia may affect cellular proliferation and organ development resulting in growth restriction [79].

Second, placental morphology and function can be altered by iron deficiency. Research has connected maternal anemia with decreased placental vascularization, impaired nutrient transportation and increased oxidative stress. Such changes compromise nutrient delivery to the fetus and may negatively affect birth outcomes [80].

Third, iron is important for brain development in the fetus. Iron is required for myelination, neurotransmitter synthesis and neuronal differentiation. Therefore, maternal iron deficiency at critical periods of development has been associated with long-term cognitive, behavioral and neurodevelopmental deficits in the offspring [81].

New nutrigenomic evidence indicates that genetic variation may influence the impact of iron deficiency on fetal growth. Genetic variation that affects iron absorption, transport and storage may influence maternal susceptibility to anemia and may affect fetal response to maternal iron status. For example, polymorphisms in TMPRSS6 have been associated with reduced iron intake and an increased risk of iron deficiency anemia despite adequate dietary intake [82].

Polymorphisms in genes of transferrin and transferrin receptor may also affect the efficiency of iron transport in the placenta thus impacting on the fetal iron acquisition and developmental outcomes. These results demonstrate the role of gene–nutrient interactions in the heterogeneity of pregnancy outcomes among women exposed to similar nutritional environments [83].

➢ *Iron Supplementation & Precision Nutrition Approaches*

Iron supplementation remains a cornerstone of antenatal care globally, with the World Health Organization recommending that all pregnant women in settings with a high prevalence of anemia be offered iron supplementation. Daily supplementation with iron and folic acid has been

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

shown to reduce maternal anaemia, improve iron stores and reduce the risk of low birth weight and preterm birth [70].

But new evidence shows that people have very different reactions to iron supplements. Variability may be due to genetic factors that affect iron absorption, hepcidin regulation, and iron transport. Therefore, precision nutrition approaches aim to identify genetic markers to guide individualized supplementation strategies [84].

In the future, nutrigenomic interventions may allow healthcare providers to identify women who are at increased risk of iron deficiency based on their genetic profiles and tailor supplementation accordingly. Such strategies could improve the efficacy of interventions while reducing the risk of excess iron supplementation such as oxidative stress and vulnerability to infection [85].

### *C. Polymorphisms of the Vitamin D Receptor (VDR)*

➢ *Vitamin D and Maternal-Fetal Wellbeing*

Vitamin D is fundamentally involved in calcium and phosphorus homeostasis, skeletal mineralization, immune regulation, placental function and fetal development. Adequate vitamin D status during pregnancy is important for maternal bone health, placental development, calcium transfer to the fetus and optimal fetal skeletal development. There is growing evidence that vitamin D deficiency during pregnancy is related to adverse maternal and neonatal outcomes such as gestational diabetes, preeclampsia, preterm birth, low birth weight, impaired fetal bone development and neonatal hypocalcemia [86].

Vitamin D can be taken in through diet and supplements, but approximately 80–90% of circulating vitamin D is produced in the skin from exposure to ultraviolet B (UVB) radiation. The biologically inactive precursor is then sequentially hydroxylated in the liver and kidneys to give 1,25-dihydroxyvitamin D [1,25(OH)2D], the hormonally active form of vitamin D [87]. This active metabolite acts physiologically mainly through binding to the Vitamin D Receptor (VDR), a nuclear transcription factor controlling the expression of hundreds of genes implicated in mineral metabolism, immune responses, cellular differentiation and fetal development.

Genetic variations that affect VDR function may, therefore, have a major role in the individual response to vitamin D and may contribute to variability in maternal and fetal health outcomes.

➢ *Vitamin D Receptor (VDR) Gene and its Role*

The Vitamin D Receptor (VDR) gene is located on chromosome 12q13.11 and encodes the vitamin D receptor protein that mediates the biological effects of active vitamin D. The VDR, together with 1,25(OH)2D, forms a heterodimer with the retinoid X receptor (RXR). This complex binds to vitamin D response elements (VDREs) in DNA to regulate transcription of target genes involved in calcium absorption, bone mineralization, immune modulation and placental development [88].

The VDR is expressed broadly in many tissues including:

- Placentas
- Womb
- Ovaries
- Bone tissue
- Cells of the immune system
- Foetal tissues

This common distribution emphasizes the importance of vitamin D signaling during pregnancy and fetal development [89].

Numerous common VDR polymorphisms have been extensively studied:

- FokI (rs2228570)
- BsmI (rs1544410)
- ApaI (rs7975232)
- TaqI (rs731236)

Such polymorphisms may affect receptor activity, gene transcription efficiency, and cellular responses to vitamin D, thereby influencing pregnancy outcomes and fetal growth [90].

➢ *VDR Polymorphisms and Maternal Bone Health*

Pregnancy places considerable strain on maternal calcium metabolism. During pregnancy, calcium transfer from mother to fetus is approximately 25–30 grams, with the majority of calcium transfer occurring in the third trimester when fetal skeletal mineralization is accelerated [91]. To meet these demands, maternal physiologic adaptations include increased intestinal calcium absorption, increased vitamin D activation and changes in bone remodeling mechanisms.

The VDR-mediated signaling of vitamin D is pivotal for these adaptations. VDR-mediated gene regulation promotes intestinal calcium absorption and calcium homeostasis necessary for maternal skeletal integrity. Genetic polymorphisms affecting VDR activity may reduce efficiency of calcium absorption and increase the risk of vitamin D deficiency and demineralization of bone tissue in pregnancy [92].

Some studies have demonstrated links between VDR polymorphisms and changes in maternal bone mineral density (BMD). For example, polymorphisms such as FokI have been associated with changes in receptor activity and calcium metabolism. Certain genotypes of VDR have been linked to lower BMD, increased bone turnover, and higher risk of osteoporosis at later age [93].

During pregnancy, inadequate vitamin D signaling related to unfavorable VDR genotypes may contribute to:

- Maternal vitamin D deficiency
- Decreased calcium absorption
- Enhanced bone resorption

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

- Pregnancy-induced bone loss
- Higher risk of osteopenia

These effects may be especially important in women with low dietary calcium intake or low vitamin D status [94].

Despite the high prevalence of nutritional challenges, research into maternal bone health has not been extensively studied in Sub-Saharan Africa. Theoretically, the abundance of sunlight is sufficient for the adequate synthesis of vitamin D. However, various studies have increasingly reported vitamin D insufficiency in pregnant women which is attributed to urbanization, indoor lifestyle, skin pigmentation, cultural practices and dietary inadequacy. Thus, knowledge of the interaction between VDR genetics and vitamin D status may be helpful for identifying women with increased risk of adverse skeletal outcomes during pregnancy [95].

➢ *VDR Polymorphisms and Fetal Skeletal Development*

Adequate maternal vitamin D status and effective placental calcium transport are critical for fetal skeletal development. Vitamin D plays an important role in fetal bone formation via regulation of calcium and phosphate metabolism, osteoblast differentiation, cartilage maturation and skeletal mineralization [96].

The placenta is known to express VDR and vitamin D-metabolizing enzymes and thus can locally regulate vitamin D signaling during pregnancy. These mechanisms permit maternal vitamin D status and VDR-mediated gene expression affect fetal growth and skeletal development [97].

VDR polymorphisms may influence fetal bone parameters by modifying the biological response to vitamin D. Several observational studies have reported associations between maternal VDR variants and differences in:

- Bone mineral content in neonates
- Length at birth
- Birthweight
- Growth of fetal femur
- Skeleton mineralization

For example, certain VDR genotypes have been linked with reduced fetal bone mass and neonatal bone mineral density, especially when maternal vitamin D status is poor [98].

There is also evidence that maternal vitamin D deficiency may influence fetal skeletal development by altering calcium transfer across the placenta. Limited availability of calcium can impair bone mineralization, lead to neonatal hypocalcemia, defective skeletal growth and low bone mass in infancy [99].

Beyond skeletal outcomes, emerging studies suggest that vitamin D signaling may affect fetal immune development, lung maturation, and metabolic programming. Thus, the implication of VDR polymorphisms could be more extensive in long-term health of the offspring than only in bone development [100].

➢ *Vitamin D Supplementation and Approaches to Precision Nutrition*

Vitamin D supplementation during pregnancy is an important public health initiative to improve maternal and neonatal outcomes . Several clinical trials have shown that vitamin D supplementation improves maternal vitamin D status, fetal growth parameters, and decreases the risk of some pregnancy complications [101].

However, there is a large inter-individual variability in response to supplementation. Some women reach adequate vitamin D levels on standard doses, while others remain deficient despite supplementation. Genetic differences in VDR and other vitamin D pathway genes may explain these differences in part [102].

VDR polymorphisms are promising biomarkers for personalized maternal nutrition interventions from a nutrigenomics perspective. In the future, precision nutrition approaches could involve the use of genetic information to identify women who may benefit from higher intakes of vitamin D, more intensive monitoring or tailored supplementation regimens in pregnancy [103].

Routine genetic screening for VDR polymorphisms is not currently recommended in antenatal care; however, ongoing advances in genomic medicine may enable more personalized maternal nutrition strategies in the future. These approaches may be especially relevant in settings with high burdens of maternal undernutrition and limited health-care resources.

*D. Interactions Between Zinc, Selenium and Other Micronutrients*

➢ *Maternal-Foetal Health and Micronutrients*

Micronutrients are vitamins and minerals that are needed in small amounts to carry out normal physiological, metabolic, immunological and developmental functions. Adequate intake of micronutrients during pregnancy is essential for maternal health, placenta function, fetal development, and pregnancy outcomes. Micronutrient deficiencies are still highly prevalent in many low and middle-income countries, especially in Sub-Saharan Africa where food insecurity, low dietary diversity, infectious diseases and socioeconomic challenges contribute to widespread nutritional inadequacies [104].

Of the many micronutrients required during pregnancy, zinc and selenium have attracted much attention due to their roles in immune regulation, antioxidant defense, cellular growth, gene expression, and fetal development. Recent nutrigenomic findings suggest that genetic differences in micronutrient metabolism and transport could influence individual nutritional needs and impact on pregnancy outcomes. These results underscore the relevance of gene–nutrient interactions for maternal-fetal health and are in line

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

with the growing interest in approaches for precision nutrition to optimize pregnancy outcomes [105].

➢ *Genetic Interactions and Zinc Homeostasis*

Zinc is an essential trace element involved in >300 enzymatic reactions and many biological processes such as DNA synthesis, RNA transcription, protein synthesis, cell division, immune function, and embryonic development [106]. During pregnancy there is a marked increase in the requirement for zinc due to rapid cellular proliferation to support maternal tissue growth and placental development and fetal organogenesis.

Zinc is also a component of the structure of many transcription factors (named zinc-finger proteins) that regulate gene expression and cellular differentiation. Therefore, unavailability of zinc can interfere with important developmental pathways and hinder fetal growth [107].

There are several genes involved in the absorption, transport and cellular homeostasis of zinc. Two major families of transporters are of particular importance:

- ZIP (Zrt/Irt-like Protein; SLC39 family) transporters that increase the import of zinc into cells.
- ZnT (SLC30 family) transporters that control the intra-cellular distribution and export of zinc.
- Genetic polymorphisms that affect these transport systems may alter zinc bioavailability and influence susceptibility to zinc deficiency [108].

Some studies have linked variation in zinc transporter genes with impaired immune responses, altered inflammatory regulation and adverse pregnancy outcomes. However, evidence is still limited especially among African populations which emphasizes the need for further studies on population specific zinc-related genetic variants [109].

➢ *Selenium Metabolism and Genetic Interactions*

Selenium Another important trace element is selenium which plays important roles in antioxidant defense, immune regulation, thyroid hormone metabolism, and reproduction. Selenium acts biologically through incorporation into a class of proteins called selenoproteins, which contain the amino acid selenocysteine [110].

Examples of important selenoproteins are:

- Glutathione peroxidases (GPX)
- Thioredoxin reductases (TXNRDs)
- Selenoprotein P (SELENOP)

These proteins protect cells from oxidative stress by neutralizing reactive oxygen species and maintaining redox balance [111].

Pregnancy is associated with increased oxidative stress due to increased metabolic activity, rapid placental growth and increased oxygen consumption. Therefore, adequate selenium status is important to protect maternal and fetal tissues from oxidative damage [112].

Genetic polymorphisms in selenium-related genes, especially GPX1, GPX4, SELENOP and SEP15 are potential modifiers of selenium utilization and antioxidant capacity. These differences may influence susceptibility to pregnancy complications related to oxidative stress, such as preeclampsia, miscarriage, and fetal growth restriction [113].

Low maternal selenium concentrations have been associated with increased risks of adverse pregnancy outcomes in several studies. Although there is sparse evidence of selenium related genetic variants, new studies suggest that gene–selenium interactions may play a significant role in maternal-fetal health [114].

➢ *Micronutrients and Immune System*

The maternal immune system undergoes massive changes during pregnancy, protecting against infection, while maintaining tolerance for the developing fetus. These immunological processes are known to be modulated by micronutrients.

➢ *Zinc and Immune Modulation*

Zinc is a well-known critical regulator of innate and adaptive immune system. It affects:

- T-cell development & function
- Maturation of B-cells
- Cytokine generation
- Activity of natural killer cells.
- Antioxidant defense systems

Zinc deficiency reduces cellular and humoral immune response, leading to increased susceptibility to infections and inflammatory disorders [115].

Maternal zinc deficiency during pregnancy has been linked to increased risk of prolonged infections, placental dysfunction and adverse birth outcomes. Infections continue to be a major cause of maternal and newborn morbidity in Sub Saharan Africa, thus adequate zinc status is of particular importance [116].

➢ *Regulation of the Immune System and Selenium*

Selenium plays a role in immune function by offering antioxidant protection and modulating inflammation. Selenoproteins reduce oxidative stress, modulate cytokine signaling, and support immune cell function. Selenium deficiency has been linked to impaired immune responses, increased inflammation, and increased susceptibility to infectious diseases [117].

Emerging data suggest that adequate selenium status may be beneficial in reducing inflammatory pathways involved in pregnancy complications such as preeclampsia and gestational hypertension. Moreover, selenium-dependent antioxidant systems are implicated in the protection of

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

placental tissues from oxidative damage during the whole pregnancy [118].

➢ *Micronutrients and Pregnancy Results*

Growing evidence suggests that zinc, selenium and other micronutrients are associated with important maternal and neonatal outcomes.

➢ *Intra-Uterine Growth Retardation and Low Birth Weight*

Maternal zinc deficiency has been linked to poor fetal growth, low birth weight and intrauterine growth restriction. Zinc is essential for the synthesis of DNA, the proliferation of cells and the production of proteins; thus, insufficient availability of zinc may negatively affect the development and growth of fetal tissues [119].

Likewise, selenium deficiency may result in disrupted placental function and oxidative stress, which negatively impact fetal growth and development [120].

➢ *Preterm Birth*

Several observational studies have found associations between low maternal zinc concentrations and increased risks of preterm birth. Zinc deficiency can impair immune regulation and increase susceptibility to infections leading to preterm birth [121].

The evidence for selenium and preterm birth is less consistent, but some studies suggest that adequate selenium status may help to maintain normal pregnancy duration through its antioxidant and anti-inflammatory effects [122].

➢ *Preeclampsia*

Preeclampsia is characterized by hypertension and systemic endothelial dysfunction in pregnancy. Its pathogenesis is believed to be based on oxidative stress. Selenium-dependent antioxidant enzymes are involved in the detoxification of reactive oxygen species, and low selenium status has been suggested as a possible risk factor for pre-eclampsia [123].

Meta-analyses have shown that selenium levels are lower in preeclamptic women as compared to healthy pregnant controls. Similar associations were found for zinc deficiency, indicating that multiple micronutrient deficiencies may contribute to the development of disease [124].

➢ *Neonatal and Infant Results*

Pregnancy micronutrient deficiency can have long-term consequences for offspring health. Insufficient exposure to zinc and selenium during fetal development has been associated with defective immune maturation, increased susceptibility to infection, altered neurodevelopment, and suboptimal growth during infancy and childhood [125].

➢ *Other Micronutrient-Gene Interactions*

Other micronutrients have gene–nutrient interactions relevant to maternal-fetal health other than zinc and selenium.

➢ *Iodized Salt*

Iodine is critical for the production of thyroid hormones and fetal neurodevelopment. Genetic variants in thyroid hormone metabolism may be involved in susceptibility to iodine deficiency disorders in pregnancy [126].

➢ *Vitamin A*

Vitamin A is important in embryogenesis, immune function and visual development, and regulates gene expression via retinoic acid receptors. Both deficiency and excess of vitamin A intake have adverse effects on fetal development [127].

➢ *Choline*

Choline is a contributor to one-carbon metabolism and DNA methylation. Genetic polymorphisms in genes involved in choline metabolism, such as PEMT and CHDH may modulate the choline requirement in pregnancy and fetal neurodevelopment [128].

➢ *Implications for Precision Nutrition*

The emerging understanding of micronutrient–gene interactions has important implications for the field of precision nutrition. Genetic differences might, in part, explain why some women develop deficiencies or poor pregnancy outcomes when exposed to the same diet. Future nutrigenomic approaches may help to provide individualized micronutrient recommendations according to genetic susceptibility, metabolic characteristics and nutritional status [129].

*E. Epigenetic Changes During Pregnancy*

➢ *Epigenetics and Materno-Fetal Health*

Epigenetics is the study of heritable changes in gene expression that do not involve changes to the underlying DNA sequence. These modifications determine the timing and mode of gene activation or silencing and are crucial in embryo development, cell differentiation, organogenesis, and physiological adaptation [130]. Epigenetic mechanisms represent an important link between the maternal environment and the genetic programming of the fetus during pregnancy. Maternal nutrition, lifestyle, infections, and environmental factors can affect fetal development and long-term health.

In the emerging field of nutritional epigenetics, nutrients have been shown to directly modulate epigenetic processes and influence gene expression at critical developmental windows. Fetal development is characterized by high biological plasticity, and epigenetic modifications occurring during gestation can persist throughout life and influence susceptibility to communicable and non-communicable diseases [131]. These observations contribute a critical element to the Developmental Origins of Health and Disease (DOHaD) paradigm that early-life environmental exposures influence later health trajectories.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

The principal epigenetic mechanisms are:

- DNA methylation
- Modifications of histones
- Regulation of noncoding RNAs

Of these mechanisms, DNA methylation has been the most studied in maternal-fetal nutrigenomics because of its direct link to nutrient availability and fetal programming [132].

➢ *DNA Methylation*

DNA methylation is the addition of a methyl group ($-CH_3$) to cytosine residues, mainly at cytosine-phosphate-guanine (CpG) sites in DNA. The process regulates gene activity by affecting the accessibility of transcriptional machinery to certain parts of the genome. Increased methylation generally inhibits gene expression whereas decreased methylation can enhance gene transcription [133].

The regulation of the epigenetic type affects the process of transcription and can be written as:

Epigenetic modifications require methyl groups supplied by a biochemical pathway called one-carbon metabolism and, therefore, DNA methylation is very dependent on one-carbon metabolism. This pathway contains several important nutrient components:

- Folic acid
- Vitamin $B_{12}$ (Cobalamin)
- Choline
- Methionine
- Betaine
- $B_6$ vitamin

These nutrients support the production of S-adenosylmethionine (SAM), the main methyl donor used in DNA methylation reactions [134].

The normal epigenetic programming of the fetus during pregnancy requires sufficient intake of methyl-donor nutrients by the mother. Deficiencies can disrupt methylation patterns and change gene expression in developing tissues and organs. Such changes can impact fetal growth, immune development, neurodevelopment, metabolic function and susceptibility to disease later in life [135].

One of the most striking examples of the importance of prenatal DNA methylation comes from studies of the Dutch Hunger Winter (1944–1945). Those exposed to famine in early gestation showed persistent changes in DNA methylation decades later, especially in genes related to growth and metabolism. These epigenetic changes have been associated with increased risk of adult obesity, cardiovascular disease, hypertension and type 2 diabetes [136].

Similarly, there is evidence from other populations that maternal nutrition influences methylation in genes involved in:

- Insulin signaling
- Lipid metabolism
- Immune modulation
- Neurodevelopmental
- The placenta's role

These findings provide strong evidence that maternal nutrition can have long-term biological effects via epigenetic mechanisms [137].

➢ *Non-Coding RNAs and Histone Modification*

While DNA methylation is the most studied epigenetic mechanism, histone modifications and non-coding RNAs also have important roles in fetal development.

Histones are proteins that DNA wraps around to form chromatin. Chemical modifications of histones, including acetylation, methylation, phosphorylation, and ubiquitinylation, influence chromatin structure and regulate gene accessibility. Nutritional factors can modulate these processes through changing the availability of substrates and cofactors for histone-modifying enzymes [138].

Non-coding RNAs, especially microRNAs (miRNAs), control gene expression by modulating messenger RNA stability and translation. Maternal diet has been shown to influence microRNA expression profiles in placental and fetal tissues and therefore modulate developmental pathways involved in growth, metabolism and immune function [139].

This combination of epigenetic mechanisms provides a highly responsive regulatory framework through which maternal environmental exposures can influence fetal developmental outcomes.

➢ *Maternal Nutrition and Fetal Programming*

Fetal programming is the process by which environmental influences during critical periods of development induce permanent structural, physiological and metabolic changes. Maternal diet is one of the most powerful determinants of fetal programming, since nutrients directly affect cellular growth, gene expression and epigenetic regulation [140].

The DOHaD hypothesis is based on the concept of fetal programming, where nutritional exposures in utero impact disease susceptibility throughout the life course. Within this framework, the fetus adjusts to nutritional cues coming from the maternal environment. Such adaptations may enhance short-term survival but increase vulnerability to chronic diseases if postnatal conditions do not match prenatal expectations [141].

➢ *Maternal Under nutrition*

Maternal undernutrition still exists in many parts of Sub-Saharan Africa and has profound effects on fetal programming. Inadequate intake of energy, protein and key micronutrients can change the way the fetus grows and cause epigenetic changes that influence health outcomes throughout life.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

Research has tied prenatal undernutrition to increased risks of:

- Low birth weight
- Growth stunting
- Poor cognitive development
- High blood pressure
- Diabetes mellitus type 2
- Heart disease

These associations are thought to be partly due to nutrition-induced epigenetic changes in metabolic and endocrine pathways [142].

➢ *Maternal Overnutrition*

Maternal obesity and excessive gestational weight gain might also affect fetal programming. Overnutrition exposes the developing fetus to elevated levels of glucose, lipids, inflammatory mediators and hormones that may induce epigenetic changes associated with metabolic dysfunction.

Research has shown that maternal obesity can change the DNA methylation patterns of genes related to:

- Control your appetite
- Adipogenesis
- Insulin signaling
- Metabolism of energy

Such changes can increase the susceptibility of the offspring to develop obesity, metabolic syndrome and diabetes later in life [143].

➢ *Deficiencies of Micronutrients*

Deficiencies of folate, vitamin B12, iron, zinc, iodine, vitamin D and choline have been associated with alterations in fetal epigenetic programming. Because many of these nutrients are directly involved in methylation pathways, deficient intake can impair normal gene regulation at critical developmental stages [144].

For example, inadequate folate intake can impair DNA methylation processes, thus increasing the risks of neural tube defects and abnormal fetal development. Choline and vitamin B12 deficiencies may also influence neurodevelopmental pathways and cognitive outcomes in offspring [145].

➢ *Maternal Epigenetics and Nutrition in the Placenta*

The placenta is a key mediator of the relationship between maternal nutrition and fetal growth. In addition to its role in nutrient transfer, the placenta is an endocrine and epigenetic organ, which can adapt dynamically to maternal environmental conditions.

Placental: maternal nutritional exposures may affect

- Patterns of DNA methylation
- expression profiles of genes
- Nutrient transmembrane transporter activity
- Signaling inflammatory pathways

These adaptations influence the delivery of nutrients to the fetus and are involved in the processes of developmental programming [146].

Recent work has demonstrated links between maternal diet quality and epigenetic modifications in genes involved in fetal growth, immune regulation and metabolic development in the placenta. Therefore, placental epigenetics has been a major research focus in the contemporary maternal-fetal nutrigenomics [147].

➢ *Implications for Precise Nutrition*

Maternal nutrition affects the long-term health of offspring through a biological mechanism called epigenetic modifications. But unlike genetic variations, many epigenetic changes are potentially modifiable by nutritional intervention, making them attractive targets for preventative health strategies.

Advances in nutrigenomics and epigenomics suggest that epigenetic biomarkers may be used in future precision nutrition strategies to identify women at higher risk for adverse pregnancy outcomes and personalize nutritional interventions accordingly [148].

## V. CURRENT RESEARCH LANDSCAPE ON NUTRIGENOMICS IN SUB-SAHARAN AFRICA

### *A. Geographic Distribution and Available Studies*

➢ *Nutrigenomics Research in Sub-Saharan Africa: A Review*

Nutrigenomics is booming worldwide, but research into gene-nutrient interactions in Sub-Saharan Africa (SSA) is scarce. Most nutrigenomic evidence comes from Europe, North America and Asia, where genomic infrastructure, research funding, biobanks and precision medicine initiatives are more developed [149]. In comparison, African populations are still highly under-represented in genomic and nutrigenomic studies, while they host the greatest human genetic diversity in the world [150].

In the last 20 years, there has been a growing appreciation of the genetic diversity found in Africa that has led to several large-scale genomics projects such as the Human Heredity and Health in Africa Consortium that have helped to increase genomic research capacity significantly across the continent. Although most of the H3Africa projects are targeted on infectious diseases, cardiometabolic disorders and population genetics, they have established important bases for future nutrigenomics investigations [151].

Currently, the nutrigenomics studies in SSA are primarily focused on:

- MTHFR polymorphisms, folate metabolism
- Iron metabolism and genes involved in anemia
- Genetics of the vitamin D pathway
- Genes and obesity and cardiometabolic risk

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

- Epigenetic effects of maternal diet
- Deficiencies of Micronutrients and Developmental Results

However, the published evidence is relatively limited in volume compared with other world regions [152].

➢ *Geographical Distribution of the Studies*

The existing literature indicates that there is a significant geographic imbalance across Sub-Saharan Africa. Research activity is concentrated in a few countries with relatively stronger research infrastructure and international collaborations.

➢ *South Africa*

South Africa has a significant proportion of the nutrigenomics publications in SSA. Research institutions that have made significant contributions to studies examining include the University of Cape Town, Stellenbosch University and the University of the Witwatersrand,

- Genetics of obesity
- Nutritional epidemiology
- Epigenetics
- Deficiencies of Micronutrients
- Cardiometabolic Disorders

South Africa's relatively developed genomic infrastructure has facilitated greater involvement in international nutrigenomics research initiatives [153].

➢ *Ghana*

Population-based studies from Ghana have become key contributors to nutritional genomics research, particularly in the study of:

- Diseases of metabolism
- Transitions in Nutrition
- Obesity proneness
- Gene-environment interaction

Research conducted through the University of Ghana and international collaborations have provided valuable insights into genetic influences on nutrition-related chronic diseases [154].

➢ *Kenya*

Kenyan studies have concentrated on:

- Nutrition of mothers and children
- Vitamin D insufficiency
- Metabolism of micronutrients
- Development of health

Several studies have examined the relation between nutritional status and genetic factors in pregnant women and children, contributing to the understanding of developmental programming in African populations [155].

➢ *Nigeria*

There is a growing body of literature in Nigeria on:

- Mother's nutrition
- Deficiencies of Micronutrients
- Nutrition and Sickle Cell Disease
- "Cardiometabolic conditions
- Genetic factors in disease susceptibility

However, the number of dedicated nutrigenomics studies specifically addressing maternal-fetal health is still relatively small given the size of the country's population and disease burden [156].

➢ *Other Nations*

Smaller numbers of nutrigenomics studies have been reported from.

- Ethiopia
- Tanzania
- Uganda
- Cameroon
- Malawi
- Burkina Faso
- Senegal

Many of these studies have been performed in the context of multinational collaborations rather than within individual national research programs [157].

➢ *Key Research Themes*

In SSA, nutrigenomics research is generally grouped into four broad categories:

- Genetic predispositions and deficiencies in micronutrients.
- Nutrition in pregnancy and infancy.
- Non-communicable diseases and obesity.
- Developmental health and epigenetic programming

One of the least explored areas, however, is maternal-fetal nutrigenomics, despite the high burden of maternal and neonatal morbidity in the region.

*B. Key Findings from African Populations*

➢ *Genetic Diversity and Responses to Nutrition*

One of the most important results of African genomics studies has been the astonishing genetic heterogeneity found in African populations. Populations in Africa have greater genetic variation than those on any other continent, resulting in considerable heterogeneity in nutrient metabolism, disease susceptibility and physiological responses to nutritional interventions [158].

"Such diversity means that nutritional recommendations based predominantly on European or North American populations may not always be relevant to African populations. Thus, there is growing recognition of the need

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

for context-specific nutrigenomic evidence for efficacious public health nutrition policies in SSA [159].

➢ *MTHFR Variants and Folate Metabolism*

Several studies in Africa have investigated MTHFR polymorphisms and their implications for folate metabolism. In general, results indicate that the MTHFR C677T mutation is less common in many African populations than in European and Asian populations [160].

But folate deficiency remains prevalent in many SSA countries because of:

- Poor dietary diversity
- Hunger
- Weak coverage of supplementation
- Poor food fortification programs

Even among populations with a low prevalence of high risk MTHFR variants, low folate intake has been shown to be a major contributor to adverse pregnancy outcomes such as neural tube defects and fetal growth restriction [161].

➢ *Anemia and Iron Metabolism*

Maternal anaemia remains a major public health problem across SSA. Research suggests there is an interaction between genetic factors and environmental exposures that influences iron status and risk of anemia.

Associations have been found with:

- Hemoglobinopathies
- Iron TransportGenes
- Pathways of inflammation
- Genetic adaptations to malaria

Nutritional deficiencies and infectious diseases are present and confound the interpretation of gene-nutrient interactions with iron in African populations [162].

Emerging evidence indicates that genetic variants affecting iron metabolism may affect responses to iron supplementation, raising the possibilities of future precision nutrition approaches [163].

➢ *Bone Health and Vitamin D*

SSA enjoys abundant sunlight, yet vitamin D deficiency has been reported in several African populations. Research has shown that there are big differences in vitamin D status, and these are affected by:

- Skin coloration
- City building (Urbanization)
- Dietary habits
- Cultural practices
- Heredity factors

The preliminary evidence suggests that VDR polymorphisms may affect maternal vitamin D status and pregnancy outcomes, though there is limited research on African pregnant women [164].

➢ *Epigenetic Programming and Maternal Diet*

The impact of epigenetic programming is one of the most exciting results coming out of African nutrigenomics research. Associations between maternal nutritional status and epigenetic changes that influence offspring growth and metabolic health have been noted in studies of rural and urban African populations [165].

Interestingly, one study conducted in West Africa reported that the seasonal food availability to the mothers may affect the DNA methylation of the offspring. These findings provide direct evidence that maternal nutritional exposures can cause long-lasting biological changes through epigenetic mechanisms [166].

These studies provide strong support for the DOHaD framework and emphasize the significance of maternal nutrition during critical periods of development.

➢ *Obesity, Cardiometabolic Disease, and Nutrition Transition*

Rapid urbanization and dietary changes in SSA have led to a growing prevalence of obesity, hypertension, diabetes and cardiovascular diseases. Nutrigenomic studies have identified gene–diet interactions that influence the susceptibility to these conditions [167].

Some studies suggest that genetic variations in pathways related to lipid metabolism, insulin sensitivity and inflammation can interact with modern dietary patterns to increase the risk of cardiometabolic diseases. The findings emphasize the importance of personalized nutrition strategies for African populations [168].

➢ *Maternal-Fetal Nutrigenomics: Evidence to Date*

Direct evidence specifically addressing maternal-fetal nutrigenomics in SSA remains scanty. Current research is mainly focused on:

- Micronutrient status of mother
- Results of birth
- Epigenetic markers
- Developmental programming

Nevertheless, the growing body of evidence consistently indicates that maternal nutritional exposures interact with genetic and epigenetic factors in the modulation of fetal growth, birth outcomes and long-term offspring health [169].

*C. Gaps in the Current Literature*

➢ *Maternal-Fetal Nutrigenomics Research Underway*

Although there is increasing interest in nutrigenomics globally, research on gene-nutrient interactions in maternal-fetal health remain very limited in Sub-Saharan Africa (SSA). Most African studies available are focused on nutritional epidemiology, micronutrient deficiencies, infectious diseases

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

and non-communicable diseases rather than on nutrigenomic mechanisms underlying pregnancy outcomes [170]. Thus, there is a lack of evidence on the effect of genetic variation on maternal nutritional requirements, placental function and fetal growth and developmental programming in African populations.

In addition, many maternal nutrition interventions implemented across SSA are still based on generalized nutritional recommendations largely derived from European, North American and Asian populations. To what extent these recommendations would be applicable to genetically diverse African populations [171] is still unclear.

➢ *Global Genomic Research Under-represents*

African populations comprise approximately 17% of the world population but are represented by a small percentage of the participants in genomic and nutrigenomic studies. Such imbalance has resulted in significant gaps in knowledge of genetic variants affecting nutrient metabolism, micronutrient requirements, and pregnancy outcomes in African populations [172].

The underrepresentation of African genomes restricts researchers' ability to:

- Find population-specific genetic variants.
- Understand gene-environment interactions
- Develop precision nutrition strategies that are accurate.
- Translate genome findings into policies on maternal health.

The lack of representation of African populations severely restricts the generalizability of current nutrigenomic knowledge, as Africa is the continent with the highest human genetic diversity in the world [173].

➢ *Few Longitudinal Birth Cohort Studies*

Longitudinal birth cohort studies are critical for the investigation of the long-term effects of maternal nutrition on the health of offspring. Such studies enable researchers to track prenatal exposures, genetic factors, epigenetic changes, and health outcomes across the life course.

However, compared with high-income countries, SSA has few large-scale birth cohorts. However, most studies available are cross-sectional or have short follow-up periods, and therefore, the potential of establishing the causal relationship between maternal nutrition, epigenetic programming and later life disease risk is limited [174].

This limitation is particularly important for testing the Developmental Origins of Health and Disease (DOHaD) hypothesis in African populations where environmental exposures are very different from those in the regions where most of the evidence has been generated.

➢ *Absence of Epigenetic Researches*

While epigenetic mechanisms are increasingly being recognized as important mediators of fetal programming, epigenetic studies are still sparse in SSA. Previous work has focused mainly on DNA methylation patterns related to seasonal nutritional exposures and early life growth, and has been limited to a few populations [175].

Major knowledge gaps remain around:

- Epigenetics of placenta.
- Maternal Diet and Fetal Epigenomes.
- Epigenetic Biomarkers of Pregnancy Disorders.
- "Epigenetic transgenerational inheritance"
- Epigenetic responses to nutrition interventions

The increasing scope of epigenetic research is particularly relevant as epigenetic modifications are potentially modifiable pathways through which nutritional interventions may improve health outcomes.

➢ *The Need for Research on Gene-Micronutrient Interactions*

Most African nutrition studies assess nutrient deficiencies and do not consider genetic variation. Consequently, little is known about the effect of genetic polymorphisms on responses to:

- Folic acid supplementation.
- Iron supplements.
- Vitamin D interventions.
- Zinc administration.
- Selenium consumption.

Understanding these interactions may help to improve the effectiveness of maternal nutrition programs by identifying women who may need tailored interventions [176].

➢ *No Genomic Infrastructure and Biobanks*

The limited availability of genomic infrastructure poses a major challenge for nutrigenomics research in SSA. Initiatives such as the Human Heredity and Health in Africa Consortium have strengthened research capacity, but many countries still face shortages of:

- Genome labs.
- Sequencing facilities
- Tools of bioinformatics.
- Biobanks.
- Genomic scientists are educated.

Such limitations impede the generation of high-quality genomic data and constrain the potential for large-scale nutrigenomics investigations [177].

➢ *Absence of Policy Translation*

Even where nutrigenomics evidence is available, translation into maternal health policies is limited. Most SSA maternal nutrition policies are based on population-wide interventions such as iron-folic acid supplementation and food fortification without consideration of genetic variability in nutrient metabolism and responses to interventions [178]. Future research should focus on implementation science

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

approaches that bridge the gap between nutrigenomic discoveries and public health practice.

*D. Underserved Regions and Populations*

➢ *Geographic Inequalities and Research Distribution*

In SSA, research in nutrigenomics is highly concentrated in a few number of countries, notably:

- South Africa
- Ghana.
- Kenya
- Nigeria.
- Ethiopia

This means that many countries contribute little or no published nutrigenomics data, creating large regional disparities in evidence generation [179].

Countries with especially limited literature on nutrigenomics include:

- Chad
- Niger
- Central African Republic
- South Sudan
- Guinea Bissau
- Sierra Leone.
- Liberia
- Burundi
- Eritrea
- Somali

Such data from these settings are lacking and limit understanding of the interaction of nutritional and genetic factors in diverse African settings and populations.

➢ *Populations in Rural Areas*

Most of the genomic and nutrigenomic studies are performed in urban or peri-urban areas where the research infrastructure is more easily accessible. Therefore, populations in rural areas, who tend to have higher rates of maternal undernutrition, food insecurity and restricted access to healthcare, are still underrepresented [180].

Since rural communities make up a large proportion of the SSA population, excluding them may result in biased estimates of nutritional risk factors and genetic associations.

➢ *Indigenous and Ethnolinguistic Populations*

Africa has thousands of ethnolinguistic groups and astonishing genetic diversity. However, most nutrigenomics studies are conducted in relatively accessible populations, and there remain many indigenous communities underrepresented.

Examples are:

- Pastoral populations.
- communities of hunter-gatherers.
- Nomad groups.
- Ethnic minority populations.

These groups may have genetic adaptations to diet, metabolism and environmental exposures that are specialized and not well understood [181].

➢ *Teen Pregnancy*

Pregnancy in adolescence is prevalent in many SSA countries, but pregnant adolescents are often underrepresented in maternal nutrition research. This is a major gap as adolescents have specific nutritional requirements related to the concurrent growth of the mother and fetus [182].

Understanding how genes and nutrients interact in pregnant teens may help scientists design better ways to help this particularly vulnerable group.

➢ *Women with Multiple Nutritional Stresses*

Many women in SSA face overlapping nutritional challenges which include:

- Micronutrient deficiency.
- Food insecurity.
- Infection.
- Excess weight.
- Metabolic diseases.

However, most studies consider these factors separately and do not look at their combined effects on maternal-fetal health. Thus, there is an urgent need for research on women with multiple nutritional burdens [183].

➢ *Pregnant Women and Women Living with HIV*

HIV continues to be a disease that disproportionately impacts Sub-Saharan Africa; however, nutrigenomics studies in pregnant women living with HIV are still limited. HIV infection, antiretroviral therapy, nutritional status and genetic variation may all interact in complex ways to affect maternal and fetal outcomes [184]. This population is a priority for future nutrigenomics research given the high prevalence of HIV in many SSA countries.

➢ *Refugees, Internally Displaced Persons (IDPs) and Conflict-Affected Populations*

Conflict, displacement and humanitarian crises affect millions of people in SSA. Pregnant women in such settings are often exposed to severe nutritional deprivation, psychological stress, infectious diseases and limited access to health care.

These populations are disproportionately impacted but nutrigenomic research is not widely conducted in these populations. Fetal Programming and Nutritional Adaptation in Understanding humanitarian settings can offer useful insights for interventions in maternal and child health [185].

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

## VI. IMPACTS ON MATERNAL AND FETAL HEALTH

### A. Outcomes for Mothers

Maternal nutrition, genetic variation and epigenetic regulation interact during pregnancy to influence maternal health outcomes. With increasing nutrigenomic studies, it is becoming apparent that changes in nutrient metabolism genes can modify the risk of complications associated with pregnancy (19), particularly in settings with nutritional deficiencies and infectious disease burdens such as in Sub-Saharan Africa (SSA). Understanding these interactions is essential to improve maternal survival, and to improve precision nutrition strategies for high-risk populations [186].

➢ *Anemia*

Maternal anemia is still one of the most common nutritional disorders of pregnant women worldwide and is particularly common in SSA. According to the World Health Organization [187], anemia affects around 37–40% of pregnant women worldwide and is highest in low- and middle-income countries.

Iron deficiency is the leading cause of maternal anemia, but folate, vitamin B12, vitamin A and other micronutrient deficiencies also contribute significantly. Increased iron demand during pregnancy due to increased maternal blood volume, placental growth, and fetal development increases the risk of anemia when dietary intake is insufficient [188].

Nutrigenomic studies suggest that genetic variants in genes involved in iron metabolism such as HFE, TMPRSS6, TFR2, HAMP, and SLC40A1 may affect iron absorption, transport, storage, and utilization. Women carrying unfavorable variants may be more prone to iron deficiency, even when they share similar dietary exposures [189].

Likewise, polymorphisms that affect folate metabolism, especially those in the MTHFR gene, can disrupt one-carbon metabolism, resulting in megaloblastic anemia from decreased folate utilization and increased homocysteine levels [190].

Maternal anemia has a number of important consequences:

- Decreased physical capacity and productivity at work.
- Increased susceptibility to infections.
- Reduced immune function.
- Greater risk of postpartum hemorrhage
- Increased risk of maternal death.

The burden of anemia among pregnant women in SSA is further compounded by the co-existence of nutritional deficiencies, malaria, helminth infections, HIV infection and poor access to antenatal care [191]. There is increasing evidence that incorporation of genetic information in antenatal nutrition programs may improve identification of women at highest risk and improve effectiveness of supplementation strategies.

➢ *Preeclampsia*

Preeclampsia is a multiorgan hypertensive disorder of pregnancy defined as new-onset of hypertension and end-organ dysfunction after 20 weeks of gestation. It is still a major cause of maternal morbidity and mortality worldwide and contributes substantially to maternal deaths in SSA [192].

Although the exact etiology of preeclampsia is not fully understood, there is an increasing evidence for interactions between:

- Genetic predisposition.
- Placental insufficiency
- Oxidative stress
- Inflammation.
- Nutritional condition.

Preeclampsia risk has been associated with several nutrigenomic pathways.

➢ *Genetic Variants Related to Folate*

Elevated homocysteine levels can occur due to polymorphisms in the MTHFR gene, which can lead to endothelial dysfunction, poor placental vascularization and increased risk of preeclampsia [193].

➢ *Selenium and Pathways of Antioxidant*

Selenium-dependent antioxidant enzymes such as glutathione peroxidases play an important role in the protection of placental tissues against oxidative stress. Genetic variations in selenium metabolism may result in reduced antioxidant capacity and could contribute to disease pathogenesis [194].

➢ *Vitamin D Pathways*

Increased risks of preeclampsia have also been associated with Vitamin D deficiency and polymorphisms in the Vitamin D Receptor (VDR) gene. Vitamin D has effects on immune regulation, endothelial function, and placental development, each of which is implicated in disease pathogenesis [195].

➢ *Epigenetic Processes*

Indeed, recent studies have shown that abnormal DNA methylation patterns in placental tissue may play a role in the aberrant gene expression associated with preeclampsia. Maternal nutritional exposures may affect the epigenetic processes that may influence the susceptibility to the disease [196]. In view of the high burden of preeclampsia in SSA, nutrigenomic approaches may eventually support earlier identification of high-risk women and facilitate targeted nutritional interventions.

➢ *Gestational Diabetes Mellitus (GDM)*

Gestational diabetes mellitus is glucose intolerance that is first recognized during pregnancy. The prevalence of GDM is increasing in SSA due to increasing urbanization, dietary transitions, obesity and sedentary lifestyles [197]. Nutrigenomics studies show an interaction of genetic

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

susceptibility and maternal dietary pattern on glucose metabolism during pregnancy.

Several genes have been implicated including:

- TCF7L2
- FTO
- PPARG
- IRS1
- GCK

These genes have a role in the regulation of insulin secretion, insulin sensitivity, adiposity and glucose regulation [198].

Women who carry high-risk variants may be particularly susceptible to adverse metabolic effects associated with:

- High energy diets.
- Excessive sugar intake.
- Obesity and pregnancy.
- Micronutrient deficiency.

Emerging evidence also points to the significance of epigenetic mechanisms in gestational diabetes. Maternal hyperglycemia may induce changes in DNA methylation that may affect placental function and fetal metabolic programming, which may predispose the offspring to a higher risk of diabetes in the long term [199].

Several nutritional factors have been investigated in relation to GDM risk including:

- Vitamin D deficiency.
- Magnesium consumption.
- Dietary fibre.
- Omega-3 fatty acids
- Folate metabolism.

These nutrients may interact with genetic susceptibility to affect disease development and progression [200].

As obesity and diabetes rates rise in SSA, understanding gene–diet interactions in the prevention of gestational diabetes and its complications may become increasingly important.

➢ *Risks of Maternal Mortality*

Sub-Saharan Africa is still home to about 70% of global maternal deaths, and there are continuing problems with access to health care, nutritional deficiencies, infectious diseases and complications during pregnancy [201].

Nutrigenomics research suggests that gene–nutrient interactions that increase susceptibility to severe pregnancy complications may indirectly influence maternal mortality risk such as:

- Anemia, severe.
- Eclampsia and Preeclampsia.
- Postpartum haemorrhage
- Sepsis
- Gestational diabetes complications

For example, women with genetic variants that influence folate metabolism may be at higher risk of anemia and hypertensive disorders. Likewise, such variations that modulate iron metabolism can aggravate the severity of anemia, predisposing to bleed-related death [202].

Micronutrient deficiencies also add to maternal mortality by impairing immune function, making women more susceptible to infection and reducing their ability to cope with the physiologic demands of pregnancy and childbirth. Deficiencies of iron, folate, zinc, selenium, vitamin D, and vitamin A have all been associated with adverse maternal outcomes [203].

Epigenetic factors may also modulate maternal health via regulation of inflammatory responses, vascular function and metabolic regulation during pregnancy. Although research remains limited, these mechanisms represent important areas for future investigation in African populations [204].

➢ *Public Health Significance*

Gene–nutrient interactions and maternal health outcomes point to the need to integrate nutrition, genomics and maternal health care. Current maternal nutrition programs mostly rely on population-wide supplementation approaches, but future precision nutrition strategies may enable:

- Early identification of genetically predisposed women.
- Personalized supplementation strategies.
- Better risk stratification.
- Better prevention of pregnancy complications
- Lower rates of illness and death among mothers.

*B. Outcomes in the Fetus*

Fetal growth and development during pregnancy is a complex process, which is influenced by maternal nutrition, genetic predisposition and epigenetic modifications. Nutrigenomic studies have shown that gene-nutrient interactions during critical developmental windows can affect birth outcomes, neonatal survival, and long-term health trajectories. This knowledge is particularly relevant in Sub-Saharan Africa (SSA), where maternal undernutrition and micronutrient deficiencies remain highly prevalent, to reduce adverse fetal outcomes and improve child survival [205].

➢ *Low Birth Weight (LBW)*

Low birth weight (LBW), defined as birth weight < 2,500 grams, is a major public health concern worldwide and is disproportionately high in low- and middle-income countries. Maternal malnutrition, infectious diseases, anemia and poor antenatal care contribute substantially to the burden of LBW in SSA [206].

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

Nutrigenomic findings indicate that fetal growth is modulated by interactions between maternal nutrient availability and genes regulating placental development, nutrient transport and fetal metabolism. Genetic variations in genes involved in folate metabolism, insulin signaling, growth regulation, and nutrient transport might affect fetal responses to maternal nutritional status [207].

Several micronutrients have been associated with increased risk of LBW when deficient in the mother. These include:

- Iron
- Folic acid
- Zinc
- Vitamin D
- Selenium
- Vitamin $B_{12}$ (Cobalamin)

Iron deficiency anemia may decrease oxygen supply to the placenta and fetus, which may negatively impact fetal growth. Likewise, folate deficiency may impair DNA synthesis and cell division, leading to limited fetal growth [208].

Epigenetic modifications are also involved in LBW. Undernutrition in pregnancy can lead to alterations in DNA methylation patterns, impacting genes related to growth regulation, energy metabolism, and placental function. Such changes can result in diminished fetal growth and an increased risk of chronic diseases in later life [209].

Research in African populations shows that maternal nutritional status preconception and during pregnancy is still one of the strongest predictors of birth weight emphasizing the importance of early nutritional interventions [210].

➢ *Preterm-Birth*

Preterm birth is defined as birth before 37 completed weeks of gestation, and is one of the leading causes of neonatal morbidity and mortality worldwide. Sub-Saharan Africa has one of the highest rates of preterm birth worldwide and contributes significantly to neonatal deaths and long-term developmental disabilities [211].

Preterm birth has many causes and results from complex interactions between:

- Maternal Nutrition
- Genetic predisposition.
- Infection and inflam-mation.
- Placental insufficiency
- Exposures to the environment.

Several gene–nutrient interactions identified in nutrigenomic studies have been associated with the risk of preterm birth.

➢ *Folate Pathway*

Mutations in the MTHFR gene may impact folate metabolism and increase homocysteine concentrations. Elevated levels of homocysteine have been associated with placental vascular abnormalities, inflammation and increased risk of spontaneous pre-term delivery [212].

➢ *Zinc Deficiency*

Zinc has important roles in immune system function, antioxidant defense and in cell growth. Maternal zinc deficiency has been linked to increased susceptibility to infection and inflammatory responses that can lead to premature labor [213].

➢ *Immune Regulation and Vitamin D*

Vitamin D modulates immune responses and inflammatory pathways in pregnancy. Studies have suggested the implication of vitamin D deficiency and VDR polymorphisms in preterm birth by placental function and maternal immune adaptation [214].

➢ *Epigenetic Contributions*

There is increasing evidence that epigenetic profiles of the fetus and placenta can be modified by maternal nutritional exposures with consequences for pathways related to inflammation, endocrine regulation and the onset of labour. These changes may affect the duration of pregnancy and the timing of birth [215].

Preterm birth is a major public health problem with premature infants being at increased risk of:

- Breathing difficulty.
- Infections in the newborn.
- Neurodevelopmental disorder.
- Growth retardation.
- Chronic diseases over the long term.

➢ *Neural Tube Defects (NTDs)*

Neural tube defects (NTDs) are severe congenital anomalies resulting from failure of the neural tube to close during early embryonic development. Common NTDs are:

- Spina bifida.
- Anencephaly.
- Encephalocele.

NTDs usually occur in the first 28 days after conception, often before the pregnancy is known [216].

➢ *Folate and Neural Tube Formation*

Among the nutrigenomic relationships in maternal-fetal health, the association between folate metabolism and neural tube development is one of the most studied.

Folate is important for:

- Synthesis of DNA
- Division of cells.
- One-carbon metabolism

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

- Methylation of DNA.

Insufficient availability of folate in the early pregnancy is a major risk factor for NTDs [217].

➢ *MTHFR Gene Variants*

The MTHFR gene provides instructions for making an enzyme known as methylenetetrahydrofolate reductase. This enzyme is involved in the body's processing of folate. The activity of the enzyme is reduced by certain polymorphisms, especially C677T and A1298C, which may affect folate metabolism.

Women who have these variants may have:

- High levels of homocysteine.
- Reduced methylation capacity
- Increased risk of neural tube defects in the fetus.

Poor folate intake remains a major public health problem across SSA, irrespective of the frequency of these variants among African populations [218].

➢ *Prevention with Folic Acid Supplementation*

Folic acid supplementation and food fortification is one of the most successful examples of nutrigenomic-informed public health interventions. Adequate intake of folic acid prior to conception and in early pregnancy has been shown to prevent a significant proportion of neural tube defects [219].

Nevertheless, mandatory fortification with folic acid has not been consistently implemented in many African countries, adding to the burden of preventable NTDs.

➢ *Intrauterine Growth Retardation (IUGR)*

Intrauterine growth restriction (IUGR), also known as fetal growth restriction, is a condition in which a fetus fails to reach its genetically programmed growth potential. IUGR is associated with an increased risk for:

- Perinatal mortality.
- Complication of the neonatal period.
- "Developmental delays.
- Chronic diseases in adults.

The condition is especially common in regions affected by maternal malnutrition, poverty and infectious diseases [220].

➢ *Nutritional Factors*

Several maternal nutritional factors contribute to IUGR, namely:

- Protein-energy malnutrition.
- Lack of iron.
- Folate deficiency.
- "Zinc deficiency.
- Lack of vitamin D.

These deficiencies impair placental development and decrease nutrient delivery to the fetus resulting in restricted growth [221].

➢ *Gene-Nutrient Interaction*

Genetic variations impacting nutrient metabolism and growth regulation might influence the susceptibility to IUGR. The genes involved in the study are:

- Folate metabolism.
- Insulin-like growth factor (IGF) signalling.
- Placental transfer of nutrients.
- Regulation of oxidative stress.

Interactions of these genes with maternal nutritional status could influence trajectories of fetal growth [222].

➢ *Epigenetic Processes*

Epigenetic modifications have been increasingly recognized as important mediators of IUGR. Maternal undernutrition can change the DNA methylation pattern that influences genes involved in:

- Placental function
- Regulation of growth.
- Endocrine pathways.
- Metabolic adaptations.

These modifications may not only contribute to restricted fetal growth, but may also increase susceptibility to obesity, hypertension, cardiovascular disease and diabetes in later life [223].

➢ *Sub-Saharan Africa Relevance*

IUGR remains of great relevance to SSA because of the high prevalence of maternal undernutrition, food insecurity, infectious diseases and inadequate antenatal care. An understanding of gene-nutrient interactions related to IUGR may facilitate the identification of susceptible pregnancies and enhance nutritional interventions directed towards fetal growth and survival [224].

➢ *Implications for Maternal and Child Health Program*

The reviewed evidence clearly indicates that complex interactions between maternal nutrition, genetic variation and epigenetic regulation influence fetal outcomes. Adverse outcomes like low birth weight, preterm birth, neural tube defects and intrauterine growth restriction contribute significantly to neonatal mortality and long-term disease burden across SSA.

Future nutrigenomic approaches may aid:

- Early detection of high-risk pregnancies.
- Personalized nutrition interventions.
- Enhanced antenatal supplementation programs.
- Improved fetal growth monitoring.
- Better prevention of birth defects and developmental disorders.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

Strengthening maternal nutrition policies will be crucial for improving fetal health outcomes and reducing intergenerational health inequalities, in addition to expanding nutrigenomics research in African populations.

*C. Long-Term Health Effects in Children*

The consequences of maternal nutrition go far beyond pregnancy and birth. Emerging evidence from nutrigenomics, epigenetics and developmental biology suggests that nutritional exposures during fetal life can impact health trajectories throughout childhood, adolescence and adulthood. The Developmental Origins of Health and Disease (DOHaD) paradigm suggests that adverse intrauterine environments may elicit persistent physiological and metabolic adaptations that elevate the risk for undernutrition and chronic diseases in later life [225].

Interactions between genes and nutrients, and epigenetic changes during critical periods of development, affect the development of organs, endocrine regulation, immune function and metabolic programming. Therefore, maternal nutritional status has important implications for long-term child health outcomes, particularly in Sub-Saharan Africa (SSA) where maternal undernutrition, micronutrient deficiencies and food insecurity are still prevalent [226].

➢ *Stunting in Childhood*

Low height-for-age (childhood stunting) is one of the most important indicators of chronic undernutrition. Stunting results from repeated nutritional deprivation and infections during critical periods of growth and development, especially during the first 1,000 days of life, from conception to the second birthday of a child [227].

Sub-Saharan Africa continues to shoulder a large part of the global burden of stunting, with millions of children affected each year. Maternal nutrition before and during pregnancy has a significant impact on fetal growth and subsequent childhood growth trajectories [228].

➢ *Mechanisms of Nutrigenomics*

Research suggests that epigenetic changes affecting genes involved in: may be caused by nutritional deficiencies of the mother.

- Growth hormone signal.
- Insulin-like growth factor (IGF) pathways
- Growth of bones.
- Building muscle.
- "Metabolism of nutrient

These changes may affect postnatal growth potential and increase the risk of growth faltering in childhood [229].

Nutrients that are particularly important for programming of growth include:

- Protein source.
- Iron.
- Zinc.
- Folate.
- Vitamin A.
- Vitamin D.
- Iodine.

Pregnancy deficiencies may affect placental nutrient transfer and fetal tissue development, increasing the risk of low birth weight and subsequent stunting [230].

➢ *Evidence from African Populations*

Studies in a variety of African settings have found associations between poor maternal nutritional status and poor child growth outcomes. Maternal anemia, micronutrient deficiencies and insufficient gestational weight gain have each been linked to elevated risks of childhood stunting [231].

Emerging evidence also indicates that epigenetic modifications established in fetal life may contribute to intergenerational transmission of stunting and undernutrition, especially in resource-limited settings [232].

➢ *Risk of Obesity*

- *Developmental Origins of Obesity*

Paradoxically, adverse nutritional exposures in fetal life may increase susceptibility not only to undernutrition but also to obesity in later life. This phenomenon can be explained by developmental programming mechanisms that prepare the fetus for the expected postnatal environmental conditions [233].

If the mother does not get enough nutrition during pregnancy the fetus may adjust its metabolism to help it save energy and survive. Such adaptations may become maladaptive in the postnatal environment with abundant food availability, increasing the risk of overweight and obesity [234].

- *Epigenetic Programming of Obesity*

Many studies have demonstrated that maternal nutrition influences epigenetic regulation of genes involved in:

✓ Appetite suppression.
✓ Power consumption.
✓ Fat storages.
✓ Insulin responsiveness.
✓ Glucose metabolism.

Changes in the methylation patterns of DNA affecting these pathways may predispose offspring to excessive weight gain and metabolic dysfunction later in life [235].

Maternal obesity and excessive gestational weight gain can similarly impact fetal programming through exposure to:

✓ High blood sugar.
✓ Increased availability of lipids.
✓ Chronic Inflamation
✓ Hormonal imbalance.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

These exposures may lead to epigenetic changes that predispose to childhood obesity [236].

- *Nutrition Transition in Sub-Saharan Africa*

In many SSA countries, rapid urbanization and dietary transitions are characterized by increased consumption of

✓ Packaged Foods.
✓ Sugar-sweetened beverages
✓ High energy density diets.
✓ Saturated fat.

Hence, many countries are currently experiencing a double burden of malnutrition, with childhood stunting and obesity coexisting within the same populations and even within the same households [237].

Nutrigenomic research has suggested that developmental programming may be an important contributor to emerging obesity epidemics across SSA, with individuals exposed to fetal undernutrition potentially being particularly vulnerable to obesity when exposed to obesogenic postnatal environments [238].

➢ *Noncommunicable Diseases (NCDs)*

- *Developmental Origins of Chronic Disease*

One of the major consequences of fetal programming is the increased risk of non-communicable diseases (NCDs) later in life. Many epidemiological studies have demonstrated association of adverse prenatal nutritional exposures with increased risk of chronic diseases in adulthood [239].

The first observations by Barker and colleagues found that low birth weight was associated with increased risks of:

✓ Heart disease.
✓ Hypertension.
✓ Type 2 diabetes.
✓ Metabolic syndrome.

These observations formed the basis of the DOHaD hypothesis and triggered many studies on the mechanisms of nutritional programming [240].

- *Heart Disease*

Maternal undernutrition can cause structural and functional adaptations on:

✓ Blood vessel formation.
✓ Heart performance.
✓ The physiology of the kidney.
✓ Regulation of blood pressure.

Such alterations may increase the susceptibility to hypertension and cardiovascular disease later in life [241]. Epigenetic modifications affecting genes involved in vascular function and inflammatory regulation have been suggested to be important biological mechanisms underlying these associations.

- *Type 2 Diabetes and Insulin Resistance*

Nutritional deficiencies during prenatal development can affect pancreatic development, insulin signaling pathways, and glucose metabolism. These changes can make you more likely to have:

✓ Insulin-resistance.
✓ Impaired glucose tolerance.
✓ Type 2 diabetes.

These effects may be attributed to gene–nutrient interactions with regard to folate metabolism, one-carbon metabolism and energy regulation pathways [242].

- *Syndrome Metabolic*

Metabolic syndrome is a group of related risk factors consisting of:

✓ Abdominal obesity;
✓ Hypertension.
✓ Dyslipidaemia.
✓ Insulin-resistance.

The evidence [243] suggests that fetal nutritional exposures may modulate all the major components of the metabolic syndrome through long-term metabolic programming and epigenetic regulation.

- *Developmental Outcomes*

Maternal nutrient deficiencies might also impact neurodevelopment and cognition. Low intake of folate, iron, iodine, zinc, vitamin B12, and choline during pregnancy has been associated with:

✓ Cognitive functioning is disrupted.
✓ Difficulties in learning.
✓ Behavioral problems.
✓ Poor academic performance.

These effects may be linked to modified neuronal development and epigenetic regulation of neurodevelopmental pathways [244].

- *Implications Intergenerational Issues*

A key feature of nutrigenomic and epigenetic programming is the potential for intergenerational transmission. Biological changes can be permanent in one generation and can affect the health of next generations via nutritional exposures [245].

For example:

✓ The undernourished mother may predispose her offspring to chronic disease.
✓ Later in life these children can develop pregnancy problems.
✓ Then, similar nutritional vulnerabilites may be passed on to future generations.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

This cycle helps explain why health inequalities and malnutrition continue across generations especially in resource-limited settings [246].

- *Implications for Public Health and Policy*

The long-term consequences of fetal nutritional programming underscore the importance of investing in maternal nutrition before conception, during pregnancy and in early childhood. Improving maternal nutritional status could:

- ✓ Reduce the number of stunted children.
- ✓ Obesity and metabolic diseases can be prevented.
- ✓ Future NCD burden reduction.
- ✓ Encourage cognitive development.
- ✓ Foster better human capital outcomes.

A promising direction for tackling both undernutrition and the growing burden of non-communicable diseases in Sub-Saharan Africa lies in integrating nutrigenomics and epigenetic evidence into maternal and child health policies. However, further research in African populations is needed to better understand population-specific gene-nutrient interactions and inform context-appropriate interventions [247].

## VII. CHALLENGES TO NUTRIGENOMICS RESEARCH AND IMPLEMENTATION IN SUB-SAHARAN AFRICA

Nutrigenomics has great potential in maternal and fetal health to enhance pregnancy outcomes, optimize nutritional interventions and promote precision medicine. However, translating nutrigenomic knowledge into research, policy and clinical practice is hampered by a range of structural, financial, technical and ethical challenges across Sub-Saharan Africa (SSA). These barriers restrict the development of context-specific evidence and incorporation of nutrigenomics into maternal and child health programs [248].

### *A. Limited Genome Infrastructure*

The poor availability of genomic infrastructure is one of the major impediments to nutrigenomics research in SSA. Nutrigenomic research requires advanced laboratory infrastructure, high-throughput sequencing platforms, bioinformatics capabilities, biobanks and specialized human resources. However, resources of this kind are still very unevenly distributed across the continent, with most countries having limited capacity to perform advanced genomic analyses on their own [249].

Despite notable strides made through initiatives such as the Human Heredity and Health in Africa Consortium, genomic research infrastructure remains concentrated in a handful of countries including South Africa, Nigeria, Kenya, Ghana and Ethiopia. Consequently, many nations still depend significantly on international collaborations for genomic analyses and data processing [250].

➢ *Absence of Genomic Labs*

Nutrigenomics research needs facilities that are able to:

- DNA extraction and genotyping.
- Whole genome sequencing
- Epigenome analysis.
- Transcriptome Analysis
- Biomarker evaluation.

High costs of establishment and maintenance mean that many research institutions in SSA do not have access to these technologies. Problems with equipment maintenance, an unreliable electricity supply and lack of technical support can affect the quality and sustainability of research in laboratories that exist [251].

The lack of local genomic laboratories means that biological samples are often shipped to laboratories outside Africa, which increases the cost, delays the analyses, and raises concerns about data ownership and sovereignty.

➢ *Limited Bioinformatics Capabilities*

Modern nutrigenomics generates large and complex data sets that require sophisticated computational analysis. Bioinformatics is important in the following:

- Analysis of genomic data.
- Identification of variants
- “Epigenetic profiling.
- Integration of systems biology.
- Personalized nutrition modeling

Despite increased investments in genomic sciences, SSA still suffers shortages in trained bioinformaticians, computational biologists and data scientists [252].

This skills gap limits the ability of local institutions to analyze genomic data independently and to translate findings into meaningful applications for public health.

➢ *Biobanks and Data Repositories in Disrepair*

The storage of biological samples and the genomic studies over time are important roles played by biobanks. Large scale nutrigenomics studies often require access to:

- Maternal blood specimens.
- Tissues from the placenta.
- Samples of cord blood.
- DNA banks.
- Samples from longitudinal birth cohorts.

Many SSA countries have limited biobanking infrastructure, which limits the opportunity for long-term investigations into maternal nutrition, fetal programming and gene-nutrient interactions [253]. Similarly, African populations are not as comprehensively represented in genomic databases compared to Europe, North America, and Asia.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

➢ *Limitation of Human Resources*

Successful nutrigenomics programs require multidisciplinary expertise in:

- Scientists in nutrition.
- Geneticists.
- Molecular biologists.
- Epidemiologists
- Bioinformatics specialists.
- Public health practitioners.
- Maternal health specialists.

Many African institutions do not have specialists trained in genomic medicine and nutrigenomics. The problem of brain drain also continues to affect research capacity, with talented scientists often migrating to higher income countries for better career prospects and research support [254].

➢ *Uneven Regional Distribution*

The genomic infrastructure is unevenly distributed in SSA. The majority of premier facilities are located in urban and academic institutions, and rural and underserved areas have limited access to research facilities. This geographic disparity is one of the reasons why many populations are underrepresented in genomic studies, and it limits the ability to generalize research results across the continent [255].

➢ *Implications for Maternal Fetal Nutrigenomics*

The limited genomic infrastructure is a major barrier to maternal-fetal nutrigenomics research for the following reasons:

- Identification of population-specific genetic variants.
- Study of epigenetic mechanisms.
- Development of precision nutrition strategies.
- Translation of research results into clinical practice

Therefore, addressing infrastructure gaps is a prerequisite for the advancement of nutrigenomics-informed maternal health strategies in SSA.

*B. Insufficient Funding*

Insufficient funding is one of the most pervasive barriers to the research and implementation of nutrigenomics in SSA. Nutrigenomics is by its very nature resource intensive requiring considerable investments in laboratory infrastructure and equipment, personnel, training, data management systems and long-term cohort studies. Unfortunately, in many African countries, research funding allocations are not sufficient to fund such complex scientific endeavors [256]. Therefore, the majority of nutrigenomics projects are dependent on external funding from international organisations, charitable foundations and foreign research institutions.

➢ *Low Investment in National Research*

Many SSA countries invest less than 1% of Gross Domestic Product (GDP) in research and development, far below the internationally recommended targets [257].

Limited domestic investment affects:

- Developed in the laboratory.
- Procurement of equipment.
- Research education.
- Systems for data management.
- Availability of grant.

Thus, nutrigenomics research is often competing with more pressing public health priorities, such as infectious disease control, maternal mortality reduction, and health care delivery.

➢ *Reliance on Foreign Funding*

A large part of genomic and nutrition research in Africa is funded by external partners including:

- International Research Councils
- Development agencies
- Philanthropic Foundations
- Academic institutions in wealthy countries.

While these partnerships have generated useful scientific advances, reliance on outside funding can result in a number of challenges:

- Research priorities may be influenced by donor interests.
- The sustainability of the project may be limited.
- Local control over research agendas may be lessened.
- Capacity-building efforts might not be uniform [258]

For the long-term development of nutrigenomics in SSA, there is a need for better domestic financing mechanisms and African-led research initiatives.

➢ *Expensive Genomic Technologies*

Even as sequencing costs are falling around the globe, genomic technologies are still expensive. Key cost components are:

- Sequencing platforms
- Laboratory reagents.
- Genotyping assays.
- Software for bioinformatics.
- Data storage system.
- Maintenance of equipment.

These costs can be prohibitive for institutions with limited budgets, limiting the scale and frequency of nutrigenomics studies [259].

Furthermore, imported equipment and reagents often entail additional costs such as shipping, customs clearance, and currency fluctuations.

➢ *Limited Funding for Longitudinal Cohorts*

Longitudinal cohort studies, tracing participants from preconception or pregnancy through childhood and sometimes adulthood, are often needed in studies of maternal-fetal nutrigenomics.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

These studies are costly because they need:

- Long-term follow up of participants.
- Multiple sampling of biological material.
- Extensive data collection.
- Laboratory analyses advanced

As a result, there are relatively few large-scale birth cohorts in SSA, limiting opportunities to study developmental programming and long-term health outcomes [260].

➢ *Insufficient Support for Capacity Building*

Investing in human capital development is critical for the sustainability of nutrigenomics research. But funding for:

- Genomic training programs.
- Bioinformatics training
- Research mentorship
- Specialized graduate programs.

Remains inadequate in a number of SSA countries [261].

Without sufficient investment in workforce development, the expansion of infrastructure alone will be insufficient to establish robust nutrigenomics ecosystems.

➢ *Limited Translation to Policy and Practice*

Shortages of funding also impact on implementation and translation of policy. Even with the advent of nutrigenomics evidence, financial constraints frequently pose obstacles:

- Development of precision nutrition programs.
- Inclusion in antenatal care services.
- Genetic screening program.
- Population-level nutritional surveillance.

Many scientific findings do not translate into clinical or public health practice [262].

➢ *Strategic Priorities for Improvement*

Meeting funding challenges will require:

- More government funding for research and development.
- Creation of national genomics funding schemes.
- Expansion of public-private partnerships
- Strengthening of regional research networks.
- More support for research agendas led by Africans.
- Sustainable financing of longitudinal maternal-child cohorts

Such investments will be critical for the generation of high-quality nutrigenomic evidence and the translation of advances in precision nutrition to improve maternal and fetal health outcomes throughout Sub-Saharan Africa.

*C. Shortage of Trained Researcher*

The success of nutrigenomics development in Sub-Saharan Africa (SSA) is highly dependent on the availability of highly trained professionals who can integrate knowledge from nutrition science, genetics, molecular biology, epidemiology, bioinformatics, public health and clinical medicine. But the lack of well-trained researchers and technical personnel remains one of the biggest barriers in the region for nutrigenomics research [263].

Nutrigenomics is an inherently multidisciplinary approach requiring expertise in genomic technologies, nutritional assessment, biostatistics, computational biology and translational research. Unfortunately, many African countries face chronic shortages of professionals with these specialized skills, limiting research productivity and the translation of scientific discoveries into public health interventions [264].

➢ *Specialized Training Programs with Limited Availability*

Many universities and research institutions in SSA offer programs in nutrition, medicine and public health, but there are few opportunities for advanced training in:

- Nutrigenomics:
- Nutrigenetics.
- Genomic epidemiology
- Biomathematics.
- Epigenetics.
- Precision Nutrition

Thus, researchers in these fields often rely on international training opportunities that are accessible to a small proportion of scientists only [265].

Moreover, genomics is a new subject in many university curricula in Africa thus the exposure of undergraduate and postgraduate students is not sufficient.

➢ *Challenges of Brain Drain and Workforce Retention*

The migration of highly skilled researchers to high-income countries continues to impact scientific capacity across SSA. Talented scientists are often tempted away from local institutions by good funding opportunities, better laboratory facilities and better career prospects [266].

This brain drain phenomenon results in:

- Knowledge destruction.
- Reduced mentoring capacity.
- Slower development of local research programmes.
- External collaborators.

As a result, many institutions have difficulty maintaining research teams capable of leading large-scale nutrigenomics projects.

➢ *Bioinformatics Experts in Short Supply*

Modern nutrigenomics relies on the computational analysis of large amounts of genomic data. However,

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

bioinformatics is still one of the least developed scientific disciplines in many African countries [267].

Lack of trained bioinformaticians limits the ability of researchers to do the following:

- Analyze genomic data on its own.
- Perform genome-wide association study.
- Conduct epigenetic analyses.
- Develop predictive nutrition models.
- Translating findings from genomics into policy-relevant evidence.

This skill gap often means that data analysis has to be outsourced to collaborators outside Africa, which can slow down research outputs and hinder local capacity development.

➢ *There is a Lack of Multidisciplinary Collaboration.*

For nutrigenomics research to be effective, cooperation is needed between:

- Nutritionist.
- Geneticists.
- Obstetricians.
- Paediatrics.
- Molecular biologists.
- Epidemiologists
- Public health.

However, in many SSA settings, institutional fragmentation and limited interdisciplinary research structures can hinder such collaboration [268].

➢ *Implications for Maternal Fetal Nutrigenomics*

The limited number of qualified researchers restricts the production of African-led evidence on maternal-fetal gene–nutrient interactions and the continent's capacity to develop context-specific precision nutrition strategies. Therefore, better education, mentorship and workforce retention programs will be important for the advancement of nutrigenomics research and implementation across SSA [269].

*D. Small Biobanks and Genetic Databases*

➢ *Role of biobanks in Nutrigenomics*

Biobanks are repositories of biological specimens and health information and are important resources for genomic and nutrigenomic research. Research in maternal-fetal nutrigenomics requires access to:

- Maternal blood specimens.
- Tissues from the placenta.
- Samples of cord blood.
- DNA samples.
- Clinical longitudinal data.

Such resources allow for the study of gene–nutrient interactions, epigenetic modifications and developmental programming [270].

➢ *Weak Biobanking Infrastructure*

Despite recent developments, biobanking infrastructure is still under-developed in many SSA countries. Presently, biobanks are situated in a limited number of research institutions and often supported by international programs such as the Human Heredity and Health in Africa Consortium [271].

Challenges are:

- High operating costs.
- Storage space is tight.
- Weak cold-chain systems.
- Power supply not dependable.
- Personnel trained unavailable.

These limitations restrict the possibility for researchers to carry out large-scale and long-term nutrigenomic studies.

➢ *Under-Representation in International Genetic Databases*

Populations of Africa are home to the highest levels of human genetic diversity in the world, but are largely underrepresented in international genomic databases [272].

Most genomic reference datasets are from European, Asian, and North American populations, limiting knowledge of:

- Population-specific variants
- Gene-nutrient interaction.
- Genetic factors of pregnancy outcomes

This underrepresentation may decrease the accuracy and relevance of precision nutrition approaches based on non-African datasets.

➢ *Lack of Longitudinal Cohort Databases*

Longitudinal birth cohort studies are a valuable resource for maternal-fetal nutrigenomics research, since they permit investigators to track mothers and children over time. However, there are relatively few such repositories across the SSA [273].

The absence of long-term biological and clinical datasets restricts the possibilities to study:

- Developmental programming
- Epigenetic inheritance.
- Growth trajectories of childhood.
- Risk of future disease.

➢ *Research and Policy Implications*

The expansion of biobanks and African genomic databases will be central to producing robust evidence on maternal nutrition and fetal development. Improved

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

infrastructure can support African-led research and the development of precision nutrition interventions tailored to local populations [274].

*E. Ethical, Legal, and Social Concerns*

Genomic information is being gathered, stored, analysed and shared, raising many ethical, legal and social issues. These issues are especially important in SSA due to diverse cultural contexts, historical inequities in global research, and evolving regulatory frameworks [275]. Addressing these issues is essential to building public trust and facilitating responsible nutrigenomics research.

➢ *Issues of Informed Consent*

In genomic research, biological samples and data are often collected for future uses that may not be fully foreseeable. This creates problems in providing meaningful informed consent [276].

Participants may be concerned with:

- Secondary use of samples.
- Exchange of international information.
- Applications commercials.
- Long-term storage of the genetic information

Researchers must therefore ensure that their consent processes are transparent and culturally appropriate.

➢ *Privacy & Confidentiality*

Genetic information is uniquely sensitive in that it can reveal information not only about individual persons but also about their biological relatives and communities [277].

Possible risks include:

- Data access not permitted.
- Genetic discrimination.
- Breach of confidentiality.
- Stigmatization of specific populations

To protect the privacy of participants and to facilitate the secure management of genomic data, robust governance mechanisms are required.

➢ *Data Ownership and Benefits Sharing*

There have been previous concerns that biological samples exported out of Africa have not been sufficiently inclusive of local parties or equitably shared benefits [278].

Frequently asked questions include:

- Biological specimens ownership.
- Genomic data governance.
- Intellectual property rights
- Benefits of research distribution.

Many scholars have called for African-led systems of governance that would foster equitable partnerships and enhance local scientific capabilities.

➢ *Community and Cultural Considerations*

Genetic research may challenge cultural beliefs about ancestry, inheritance, disease causation and biological identity. If communities are not properly engaged, it can undermine trust and participation [279].

Community engagement strategies are therefore essential to:

- Advancing genomics knowledge.
- Myth-busting
- More acceptance of research.
- Encouraging ethical behavior.

➢ *Regulatory Issues*

Many SSA countries are in the process of developing legal frameworks for:

- Genomic research.
- Biobanks.
- Data availability.
- Cross border transfer of samples:

Different regulations could create uncertainties for researchers and complicate international collaborations [280].

*F. Health System Barriers*

Even if nutrigenomic discoveries are made, their use will depend on the ability of health systems to translate genomic knowledge into daily practice. Unfortunately, many health systems in SSA are severely resource-constrained, limiting preparedness for precision nutrition and genomic medicine [281].

➢ *Scarce Health Resources*

In many SSA countries, health systems are still struggling with:

- Labor shortages.
- Poor infrastructure.
- Poor diagnostic capacity.
- Supply chain problems.
- High disease burden.

In these circumstances, the provision of essential health care services takes precedence over emerging genomic technologies [282].

➢ *Conflicting Public Health Priorities*

SSA continues to face challenges in:

- Death of mothers.
- Infection.
- Malnutrition
- AIDS.
- Tuberculosis.
- Malaria.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

These urgent priorities often compete for limited healthcare resources and research funding, limiting opportunities for investment in nutrigenomics programs [283].

➢ *Restricted Access to Genetic Testing*

The availability of genetic testing and genomic screening services is a prerequisite for nutrigenomics. However, such services are still out of reach or unaffordable for many populations in SSA [284].

Barriers are:

- High price.
- Limited lab space.
- Personnel not trained.
- Geographical differences in service accessibility.

➢ *Insufficient Nutrition Surveillance Systems*

High quality nutritional and genomic data are necessary for effective precision nutrition strategies. But many countries have shoddy systems for:

- Surveillance of Nutrition.
- Monitoring of maternal health.
- Integration of genomic data.
- Electronic medical records.

These limitations hamper the identification of high-risk populations and the evaluation of nutrigenomic interventions [285].

➢ *Implementation Gaps and Policy*

In most SSA countries there are maternal nutrition policies, but these rarely consider genomics. The translation of nutrigenomic evidence into policy is still in its infancy because:

- Not enough evidence from Africa.
- No frameworks for implementation.
- Limited visibility for policymakers.
- Resource constraints [286].

➢ *Future Directions*

The implementation of nutrigenomics will require: strengthening health systems

- Genomic infrastructure investment:
- Work force development
- Expansion of laboratories services.
- Enhanced nutrition surveillance.
- Integrating genomics into maternal health programs.
- Developing policy frameworks adapted to the context.

Such efforts are critical to translate future advances in nutrigenomics into tangible improvements in maternal and fetal health outcomes across Sub-Saharan Africa.

## VIII. IMPLICATIONS FOR POLICY AND FUTURE DIRECTIONS

The increasing evidence on gene-nutrient interactions, fetal programming and precision nutrition underscores the potential of nutrigenomics to transform maternal and child health interventions in Sub-Saharan Africa (SSA). But unlocking this potential requires deliberate policy actions, investments in research infrastructure and stronger regional collaboration. The high burden of maternal malnutrition, anemia, low birth weight, stunting and emerging non-communicable diseases (NCDs) in the region, the incorporation of nutrigenomic insights into public health strategies could enhance the effectiveness of maternal nutrition programs and ultimately improve health outcomes across the life course [287].

### *A. Incorporating Nutrigenomics in the Maternal Health Policies*

➢ *Nutrition Interventions Beyond One-Size-Fits-All*

Today, maternal nutrition programs in most SSA countries are largely based on universal approaches, such as:

- Iron-folic acid supplementation
- Fortification of food.
- Supplementation with micronutrients
- Diet counseling.

These interventions have been shown to have significant benefits but generally do not consider the genetic variability that may affect nutrient metabolism, absorption and utilization [288].

Nutrigenomics provides an opportunity to move toward more personalized and evidence-based nutritional approaches because it recognizes that women may respond differently to nutritional interventions based on their genetic profiles.

For example:

- Variations in MTHFR may affect the need for folate.
- Variants affecting iron metabolism may modify responses to iron supplementation.
- Vitamin D receptor polymorphisms may affect vitamin D utilization and pregnancy outcomes.

Such evidence could provide the basis for future maternal health policies to optimize nutritional interventions and improve maternal-fetal outcomes [289].

➢ *Precision Nutrition for Prenatal Care*

Possible options for integrating precision nutrition approaches into routine antenatal services are:

- Risk stratification tools.
- Nutrition screening programs.
- Genetic risk evaluations.
- Customized nutritional guidance.

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While broad genetic screening may not be feasible in many SSA settings currently, targeted approaches could be initially used in high-risk populations and research settings [290].

As genomic technologies become more affordable, precision nutrition may be able to complement existing maternal health programs and improve prevention strategies for:

- Anaemia in pregnancy
- Pre-eclampsia.
- Gestational diabetes mellitus.
- Neural-tube defects.
- Intrauterine growth restriction.

➢ *Strengthening Food Fortification Policies*

Evidence that genes involved in folate metabolism are associated with neural tube defects supports mandatory food fortification programs. Policymakers should continue to expand access to fortified foods, while supporting research on the genetic determinants of nutrient requirements in African populations [291].

Similarly, fortification strategies that:

- Iron.
- Zinc.
- Vitamin A.
- Vitamin D.
- Iodine.

Can benefit from nutrigenomic evidence that identifies population-specific needs and responses.

➢ *Nutrigenomics in the National Nutrition Strategies*

The national nutrition policy should recognize the emerging role of genomics in maternal and child health. This can be achieved by:

- Role of genomics in nutrition policy.
- Research support for precision nutrition.
- Creating national strategies for genomic medicine.
- Encouraging collaboration between nutritionists, geneticists and politicians [292].

Such integration would help to ensure that future nutrition interventions are scientifically relevant and responsive to the evidence as it evolves.

*B. Strengthening Research Capacity*

➢ *Human Resource Development Expansion*

A sustainable nutrigenomics ecosystem requires a well-trained workforce able to perform high-quality genomic and nutrition research. Governments, universities and development partners should invest in training programmes to address:

- Nutrigenomics:
- Nutrigenetics.
- Biomathematics.
- Epigenetics.
- Genomic epidemiology
- Precision Nutrition

Building local expertise will reduce reliance on external collaborators and bolster African-led research agendas [293].

➢ *Building the Genomic Infrastructure*

Investment in infrastructure is a precondition for research capacity building. Priorities include:

- Genome labs.
- Sequencing facilities
- Biobanks.
- Data repositories.
- Computational platforms

Enhancement of these resources will improve the capabilities of African institutions to generate and analyze genomic data related to maternal and fetal health [294]. The work of the Human Heredity and Health in Africa Consortium has demonstrated the value of coordinated investments in genomic infrastructure and offers an important model for future initiatives.

➢ *Supporting Birth Longitudinal Cohorts*

Long-term cohort studies are essential to understand the relationship between maternal nutrition, genetic variation, fetal programming and risk of disease later in life.

Future investments should support:

- Pregnancy cohorts
- Mother-child cohorts.
- Systems for nutritional surveillance
- Developmental programming research.

These cohorts would provide critical information on the unique nutritional and genetic contexts of African populations [295].

➢ *African-Led Supporting Research*

Much of the genomic research in Africa has historically been funded and led from outside the continent. While international collaborations are still important, more emphasis should be put on:

- Leadership of African research.
- Local priority setting.
- Funding mechanisms for sustainability.
- Capacity development.

African-led nutrigenomics research is more likely to address region-specific maternal and child health challenges and ease translation to local policy and practice [296].

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*C. Regional Genomic Surveillance and Data Sharing*

➢ *Importance of Regional Cooperation*

A lot of SSA countries share similar maternal and nutritional challenges, which allows the possibility of regional collaboration to speed up nutrigenomics research and implementation. This is something we can tackle together:

- Bigger samples.
- Representations of diverse populations.
- Sharing of resources.
- Exchange of knowledge.
- Standardized research techniques [297].

Regional networks can also increase negotiating power for funding and improve the sustainability of research programs.

➢ *Development of African Genomic Databases*

One of the major priorities for the future is to develop comprehensive genomic databases for African populations.

Such databases can do:

- Enhance understanding of genetic diversity.
- Identify population specific variants with respect to nutrients.
- Support precision nutrition research.
- Improved interpretation of genomic results.

The exceptional genetic diversity of Africa makes the expansion of genomic reference datasets critically important to allow equitable participation in global genomic medicine initiatives [298].

*D. Regional Nutrigenomics Collaborative*

Regional nutrigenomics consortia may facilitate collaborative research on:

- Maternal Nutrition
- Gene-nutrient interaction.
- Pregnancy results.
- Developmental programming
- Growth and development in childhood.

Such networks would promote protocol harmonization, enable data pooling and improve research efficiency across multiple countries [299].

➢ *Strengthening Data Sharing Infrastructure*

Responsible data sharing of genomic and health data is essential for effective nutrigenomics research. Policymakers need to create frameworks that foster:

- Sharing data securely.
- Privacy of Participants.
- Moral governance.
- Cross-border cooperation.
- Fair sharing of benefits.

Strong governance systems are key to building public trust and maximizing the scientific value of genomic datasets [300].

➢ *Using Digital Health Technologies*

Emerging digital health platforms offer opportunities to support genomic surveillance and precision nutrition initiatives through:

- Electronic medical records.
- Nutritional surveillance systems.
- Mobile health applications
- Artificial Intelligence Assisted Data Analysis
- Integrated databases of maternal health

These technologies can enhance data quality, enable research and inform evidence-based policymaking [301].

➢ *Future Prospects*

The future of nutrigenomics in maternal-fetal health in SSA will depend on the ability of governments, researchers, healthcare systems and development partners to work collaboratively. Significant challenges remain, but progress is possible because of advances in genomic science, falling sequencing costs, growing African research capacity and growing appreciation of precision nutrition.

To harness the potential of emerging advances in precision nutrition to tackle long-standing maternal and child health challenges, SSA can integrate nutrigenomic evidence into maternal health policies, strengthen research infrastructure, and foster regional collaboration. These efforts could eventually lead to reductions in maternal mortality, childhood stunting, low birth weight and the increasing burden of non-communicable diseases across the region [302].

*E. Developing Precision Nutrition Guidelines*

The development of nutrigenomics offers the chance to shift from general nutritional recommendations to precision nutrition approaches considering genetic variation, environmental effects, diet, and physiological traits. Precision nutrition seeks to provide tailored nutritional interventions to improve health outcomes based on individual biological differences [303].

Precision nutrition guidelines could improve the success of nutritional interventions in the context of maternal and fetal health by acknowledging that pregnant women may respond differently to nutrients due to genetic and epigenetic factors. A critical step for SSA is to develop context-specific precision nutrition guidelines to improve maternal and child health outcomes while addressing the region's unique nutritional and genetic diversity [304].

➢ *Need for Context Specific Recommendations*

Most existing nutritional recommendations are based on evidence derived predominantly from European, North American, and Asian populations. Therefore, these guidelines may not completely reflect the genetic diversity,

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dietary patterns, environmental exposures and disease burdens representative of African populations [305].

Developing Africa-specific precision nutrition guidelines would help:

- Address the nutritional needs of certain populations
- Improve maternal nutrition interventions.
- Improve prevention of pregnancy complications.
- Promotes healthy fetal development.
- Reduce health inequities.

Such guidelines should be based on evidence generated from African nutrigenomic research rather than solely on extrapolation from non-African populations.

➢ *Using Genetic Risk Profiles*

Future precision nutrition guidelines could include information on genetic variants affecting nutrient metabolism, such as:

- MTHFR variants that impact folate metabolism.
- HFE variants and iron absorption.
- VDR polymorphisms and vitamin D metabolism.
- Genes associated with glucose metabolism and risk of gestational diabetes.

Identification of such variants could enable targeted nutrition recommendations for women at higher risk for adverse pregnancy outcomes [306].

➢ *Inclusion of Epigenetic Evidence*

Epigenetic studies have demonstrated that maternal nutritional exposures can affect fetal gene expression through mechanisms such as DNA methylation and histone modification. Therefore, precision nutrition guidelines should account for critical developmental windows during which nutritional interventions can have the greatest impact on fetal programming and long-term health outcomes [307].

Particular attention should be paid to:

- Nutrition before conception.
- Interventions in early pregnancy
- Adequacy of Micronutrients.
- Quality of maternal diet.

➢ *Development of Guidelines Framework*

The development of precision nutrition guidelines in SSA should include:

- Generating African nutrigenomic evidence.
- Building genomic reference datasets.
- Validation of population-specific biomarkers
- Combining nutritional and genomic data.
- Collaboration among researchers, clinicians, policy makers and communities.

This framework would ensure that guidelines are evidence-based, culturally appropriate, and feasible within local health care systems [308].

*F. Public Private Partnerships*

➢ *Significance of Cooperative Investment*

Given the high costs of genomic research and precision nutrition programmes, public-private partnerships (PPPs) can play an important role in promoting the development of nutrigenomics in SSA. Public-private partnerships are partnerships between governments, academic institutions, health care organizations, non-governmental organizations and private sector partners to achieve common public health goals [309]. Such partnerships can provide access to financial resources, technical expertise and innovation that can not be achieved through public funding alone.

➢ *Supporting Research Infrastructure*

Involving the private sector can help to:

- Set up genomic laboratories
- Sequencing facilities development
- Biobank development.
- Acquiring high technologies.
- Strengthen digital infrastructure.

Such investments can supplement government initiatives and fast track the growth of regional nutrigenomics capacity [310].

➢ *Improving Innovation and Technology Transfer*

Working with the biotechnology, pharmaceutical, diagnostic and nutrition industries can allow:

- Technology Transfer.
- Workforce Development.
- Commercialize research.
- Development of innovative nutritional products

Partnerships like these can help to close the gap between scientific discovery and practical application in maternal and child health programs [311].

➢ *Community-Based Interventions Support*

Public-private partnerships can also assist in the implementation of nutrition interventions through:

- Food fortification programs.
- Maternal supplementation programmes.
- Nutrition awareness campaigns.
- Community health outreach programs.

Proper regulation, [312] can improve the reach and sustainability of public health programs such partnerships.

➢ *Ethical and Equitable Partnership*

PPPs have significant benefits but safeguards are needed to ensure:

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- Transparency.
- Ethical behavior.
- Fair sharing of benefits.
- Protection of the rights of subjects.
- Alignment with public health priorities;

Governments and research institutions should establish governance frameworks that foster accountability and prevent conflicts of interest [313].

*G. Digital Health and Artificial Intelligence Opportunities*

➢ *The Emerging Role of Digital Health*

Digital health technologies are changing healthcare delivery and research at a rapid pace across the globe. In SSA, the rapid increase in access to mobile phones, internet connectivity and digital health initiatives provides great opportunities for the development of nutrigenomics and maternal health programmes [314].

Digital health platforms can assist:

- Surveillance of Nutrition.
- Monitoring of maternal health.
- Data Collection and Handling.
- Health education.
- Individualized nutrition counseling.

These capacities may facilitate implementation of precision nutrition interventions in resource-limited settings.

➢ *Artificial Intelligence for Nutrigenomics*

Artificial intelligence (AI) has emerged as a powerful tool for analyzing complex biological data sets. Nutrigenomics produces large amounts of genomic, dietary, clinical and environmental data, often surpassing the capacity of classical analytical methods [315].

AI technologies can help:

- Identification of gene–nutrient interaction.
- Prediction of disease risk.
- Producing personalized diet recommendations.
- Discovery of new biomarkers.
- Assisting in clinical decision making.

Machine learning algorithms can help researchers find patterns that are difficult to detect using traditional statistical methods.

➢ *AI Driven Maternal Risk Prediction*

In maternal health, AI models can be used for predicting risks of:

- Maternal anaemia
- Pre-eclampsia.
- Gestational diabetes mellitus.
- Pre-term birth.
- Intrauterine growth retardation.

The AI-driven systems could combine nutritional, genomic and clinical information to allow earlier identification of high-risk pregnancies and better targeted interventions [316].

➢ *Digital Nutrition Platforms*

In the future, precision nutrition programs may utilize digital platforms that are capable of providing:

- Individualized nutritional counseling.
- Tracking intake of nutrients.
- Pregnancy control.
- Teleconsultations.
- Teaching resources.

Mobile health applications could be especially helpful in rural and underserved communities with limited access to specialized healthcare services [317].

➢ *Strengthening Genomic Surveillance*

Digital technologies can help regional genomic surveillance efforts by:

- Electronic medical records.
- Integrated databases of genomes
- Cloud data repositories.
- Systems for sharing data across borders.

Such tools could enable large scale nutrigenomic research and improve understanding of population level genetic variation across Africa [318].

➢ *Issues and Concerns*

Digital health and AI initiatives show promise, but face several challenges in SSA, including:

- Bad digital infrastructure.
- Disparities in internet access.
- Data privacy issues.
- Regulatory uncertainty.
- Workforce Capacity Shortfalls
- Algorithmic bias from underrepresentation of African populations in training datasets [319].

Overcoming these challenges will be crucial in enabling a fair and efficient roll out.

➢ *Future Prospects*

The convergence of nutrigenomics, digital health and artificial intelligence offers unprecedented opportunities to improve maternal and fetal health in SSA. Countries in the region can leverage technological innovation, in combination with strengthened research capacity and supportive policy frameworks, to move towards more personalized, efficient and evidence-based nutrition interventions.

Despite considerable challenges, additional investment in precision nutrition, digital health infrastructure and AI-driven analytics could help reduce maternal mortality, improve birth outcomes and prevent the ever-increasing

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burden of non-communicable diseases in future generations [320].

## IX. RECOMMENDATIONS

The results of this review demonstrate the potential of nutrigenomics to improve maternal and fetal health outcomes in Sub-Saharan Africa (SSA). But realizing this potential requires a coordinated effort among governments, researchers, health providers, development partners and other stakeholders. The following recommendations are proposed to strengthen nutrigenomics research, policy integration and implementation across the region.

### *A. Suggestions to Governments*

Governments have a central role in creating enabling environments for nutrigenomics research and the translation of scientific evidence into public health practice.

➢ *Invest More in Genomics and Nutrition Research*

National governments need to spend more money on genomic science, maternal nutrition research and precision medicine programs. Increased domestic funding will lead to less dependence on external donors and foster sustainable scientific development [321].

➢ *Enhance Research Infrastructure*

Governments should focus their investments on:

- Genome labs.
- Sequencing facilities
- Biobanks.
- Tools of bioinformatics.
- National Health Data Systems:

Such infrastructure is a prerequisite for generating context-specific evidence relevant to African populations [322].

➢ *Incorporate Nutrigenomics into National Health Strategies*

Policies on maternal and child health should progressively incorporate emerging evidence on gene-nutrient interactions and precision nutrition. Policymakers should consider national frameworks for genomic medicine and personalized nutrition as part of broader health system strengthening efforts [323].

➢ *Support Food Fortification and Maternal Nutrition Program*

Existing interventions, such as folic acid fortification, iron supplementation and maternal nutrition programmes, should be strengthened while incorporating evidence from nutrigenomic research where appropriate [324].

➢ *Develop Ethical and Regulatory Frameworks*

Governments should have clear policies in relation to:

- Genomic research.
- Biobanks.
- Data security.
- Share samples.
- Ethical review.

Such frameworks are necessary to protect participants and foster responsible scientific innovation [325].

### *B. Recommendations to Researchers*

Research plays a significant role in producing evidence to inform policy and clinical practice.

➢ *Carry Out Nutrigenomics Studies Led by Africans*

There is an urgent need for locally driven studies on gene-nutrient interactions that affect maternal and fetal health in diverse African populations. Such studies should focus on nutritional challenges in the region and on genetic diversity [326].

➢ *Expand longitudinal cohort studies*

Researchers should be encouraged to start and sustain maternal-child cohort studies to examine:

- Prenatal nutrition exposures.
- Epigenetic alterations.
- Pregnancy results.
- Growth patterns in a child.
- Risks of disease over time.

Longitudinal data are required to understand the mechanisms of developmental programming [327].

➢ *Encourage Cross-Disciplinary Collaboration*

Research in nutrigenomics requires a collaboration between:

- Scientists in nutrition.
- Geneticists.
- Obstetricians.
- Pediatrics.
- Epidemiologists
- Bioinformaticians.
- Public health professionals.

Inter-disciplinary collaborations will enhance quality and translational impact of research [328].

➢ *Enhance Data Sharing and Research Networks*

To facilitate this, researchers should actively engage in regional and international genomic networks to:

- Harmonization of data.
- Exchange of knowledge.
- Sharing of resources.
- Joint analysis,

Such collaboration can speed up scientific discovery and reduce duplication of effort [329].

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

➢ *Focus on the Under-Represented*

Future research should target populations that are currently underrepresented in genomic research, such as rural communities, indigenous populations, adolescents, and vulnerable maternal groups [330].

*C. Recommendations for Health Care Providers*

Healthcare providers are important in applying nutrigenomic evidence to interventions for maternal health.

➢ *Enhance Maternal Nutrition Counselling*

Healthcare professionals should continue to provide evidence-based nutrition advice during the preconception, pregnancy, and lactation periods. Nutritional counseling should concentrate on:

- Balanced diet.
- Adequacy of micronutrients.
- Healthy weight management
- Early attendance at antenatal care [331].

➢ *Increase Genomic Awareness of Health Professionals*

Training institutions for medicine, nursing, nutrition and public health must progressively integrate genomics and precision nutrition into professional curricula. Continuing professional development programs should also be used to enhance health care workers' understanding of nutrigenomic principles [332].

➢ *Early Risk Support Identification*

Screening tools are available to health providers to identify women with an increased risk of:

- Maternal anaemia
- Micronutrient deficiency.
- Gestational diabetes mellitus.
- Pregnancy and Hypertensive Disorders.

Incorporating genomic information in the future may further refine risk stratification and personalized interventions [333].

➢ *Encouraging Community Education*

Healthcare workers should involve communities in educational activities to raise awareness of maternal nutrition, healthy pregnancy practices and the potential benefits of emerging precision nutrition approaches [334].

*D. Suggestions for development partners and donors*

Development partners and donor organizations can play an important role in supporting the growth of nutrigenomics research and implementation in SSA.

➢ *Increase Funding for Nutrigenomics R&D*

International agencies should support research efforts to:

- Maternal-fetal nutritional genomics.
- Precision Nutrition
- Epigenetics.
- Developmental programming
- Population genomics

Dedicated funding streams can speed up evidence generation and capacity building [335].

➢ *Support for Capacity Development*

Investments should be focused on:

- Training programs for research.
- Bioinformatics training
- Fellowships for genomic science.
- Laboratory enhancement.
- Mentoring programmes.

Capacity development is a prerequisite for building sustainable research ecosystems [336].

➢ *Encourage Regional Co-operation*

Development partners should support the creation of regional nutrigenomics networks and research consortia that promote collaboration among African countries.

➢ *Facilitate Transfer of Technology*

Collaborative programs should provide access to:

- Genomic technologies.
- Laboratory apparatus.
- Digital health platforms
- Artificial intelligence tools.
- Systems for data management.

Transfer of technology can enhance local ownership and reduce long-term dependence on external institutions [338].

➢ *Build Equitable Partnerships*

Funding mechanisms should support African leadership in the development, application and dissemination of research, and encourage equitable benefit sharing and the establishment of local priorities [339].

➢ *Summary Recommendation.*

To harness the full potential of nutrigenomics for improving maternal and fetal health in Sub-Saharan Africa, stakeholders should adopt a coordinated approach that combines strengthened research capacity, improved genomic infrastructure, supportive policies, enhanced workforce development, regional collaboration and sustainable financing. This will enable the region to move towards evidence-based precision nutrition approaches to address both the current maternal health challenges and the future burden of non-communicable diseases.

## X. CONCLUSIONS

Maternal and fetal health challenges continue to be a major public health problem in Sub-Saharan Africa (SSA), where high maternal mortality, anemia, micronutrient deficiencies, low birth weight, preterm birth, and childhood stunting persist as impediments to health and development.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug359

This review focuses on the emerging role of nutrigenomics in understanding the interaction between genetic variation and nutritional exposures that influence maternal and fetal outcomes. Studies of folate metabolism, iron homeostasis, vitamin D signaling, micronutrient interactions, and epigenetic programming show that gene–nutrient interactions are an important determinant of pregnancy outcomes and long-term trajectories of child health.

This review points out that maternal nutrition affects the fetus development not only through the direct nutrients, but also through the molecular mechanisms that regulate gene expression and developmental programming. Variants in genes such as MTHFR, HFE and VDR, and nutrition-sensitive epigenetic modifications have been associated with maternal anaemia, neural tube defects, impaired fetal growth, preeclampsia and gestational diabetes, and future risks of non-communicable diseases. These results bolster the tenets of the Developmental Origins of Health and Disease (DOHaD) framework, which highlights that nutritional exposures during critical developmental windows may have lifelong and even intergenerational health consequences [340,341].

There is growing global interest in precision nutrition and nutrigenomics but evidence from SSA is limited. The available studies are geographically limited, of relatively small sample sizes, and often lack long-term follow-up data. Challenges remain, including inadequate genomic infrastructure, biobanking capacity, trained researchers, funding, data sharing systems, and ethical and regulatory issues. In addition, African populations are largely underrepresented in global genomic databases, which limits the applicability of precision nutrition strategies developed from non-African populations [342,343].

However, the region offers unique opportunities for advancing nutrigenomics research due to its extraordinary genetic diversity and increasing investments in genomic science. Initiatives such as the Human Heredity and Health in Africa Consortium have demonstrated the feasibility of creating genomic research capacity and fostering regional collaboration. Scaling up such initiatives could generate robust evidence to develop population- and culturally-relevant maternal nutrition interventions [344].

The findings of this review highlight the importance of considering gene–nutrient interactions in research, policy and practice to improve maternal and child health. Future maternal health programs should go beyond generalized nutritional recommendations to evidence-informed approaches that recognize biological diversity and differential responses to nutritional interventions. Although widespread implementation of precision nutrition is a long-term goal, strengthening maternal nutrition programs today and investing in nutrigenomics research can lay the foundation for more targeted and effective future interventions [345].

To realize this vision, governments, research institutions, health systems, development partners and private-sector stakeholders will need to increase investments in genomic infrastructure, human resource development, biobanks, digital health technologies and longitudinal birth cohort studies. Strengthening regional genomic surveillance systems and promoting equitable data sharing are crucial for generating high-quality evidence and accelerating scientific discovery across the continent [346].

In conclusion, nutrigenomics is a promising frontier for improving maternal and fetal health in SSA. By building research on gene–nutrient interactions and translating emerging evidence into policy and practice, countries across the region can bolster maternal nutrition strategies, reduce adverse pregnancy outcomes and improve lifelong health prospects for future generations. Further investment, multi-disciplinary collaboration and evidence-based policy development will be essential to ensure that the benefits of nutrigenomics can contribute meaningfully towards the attainment of maternal and child health goals in Africa.

- *Proposed Final Closing Statement for the Paper*

The future of maternal and fetal health in Sub-Saharan Africa will depend not only on improving access to nutrition, but also on understanding how nutrition interacts with the unique genetic diversity of African populations. Sustained research, policy innovation, and regional collaboration can harness the potential of nutrigenomics, providing a promising pathway to precision nutrition strategies that could improve pregnancy outcomes and reduce the long-term burden of disease across generations.

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