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Unveiling the Dynamic Crosstalk between Agricultural Hazards and Spontaneous Pregnancy Loss

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Abstract- Agricultural practices expose women to a wide range of chemical, physical, and environmental hazards, which may adversely affect reproductive outcomes, particularly spontaneous abortion. This review synthesizes recent evidence (2020–2025) linking agricultural exposures—including organophosphate pesticides, herbicides, fertilizers, heavy metals, persistent organic pollutants, and occupational stressors—to miscarriage. Epidemiological studies consistently demonstrate that maternal exposure to these hazards, especially during the peri-conceptional period and first trimester, is associated with increased miscarriage risk. Mechanistic insights reveal multiple pathways by which agricultural toxins disrupt early pregnancy, including endocrine disruption, oxidative stress, placental toxicity, and immune dysregulation. Molecular genetic factors, such as polymorphisms in detoxification enzymes (e.g., PON1, GSTs), and epigenetic alterations, including DNA methylation, histone modification, and microRNA dysregulation, further modulate susceptibility and mechanistically link environmental exposures to adverse outcomes. Immunological mechanisms, including T helper cell imbalance, reduced regulatory T cells, and pro-inflammatory cytokine induction, contribute to compromised maternal–fetal tolerance. Fertilizer-related nitrate and heavy metal exposures additionally induce oxidative and epigenetic stress, highlighting the importance of cumulative and mixture effects. Overall, these findings underscore the complex interplay between environmental exposures, genetic susceptibility, and immune-epigenetic mechanisms in the etiology of miscarriage. Enhanced occupational safety, reduction of chemical exposures, and early biomarker-based risk assessment are essential to mitigate the burden of spontaneous abortion in agricultural populations. This review consolidates epidemiological, mechanistic, and molecular evidence, providing a comprehensive framework for understanding the impact of agricultural hazards on reproductive health.

Keywords: Agricultural hazards, organophosphates, fertilizers, spontaneous abortion, miscarriage, molecular genetics, epigenetics, immunology, occupational exposure.

I. INTRODUCTION

Miscarriage, defined as pregnancy loss before 20 weeks of gestation, affects approximately 10–20% of clinically recognized pregnancies worldwide. While genetic abnormalities are the most common cause, increasing attention has been directed toward environmental and occupational risk factors, particularly in agricultural settings. Modern agriculture relies heavily on chemical inputs such as pesticides, herbicides, fertilizers, and growth regulators, many of which are known reproductive toxicants (Engel et al., 2020; Torres-Rubio et al., 2020).

Women of reproductive age living or working in agricultural regions are exposed through multiple pathways, including direct occupational contact, residential proximity to sprayed fields, contaminated water sources, and dietary intake of pesticide residues (Quirós-Alcalá et al., 2021; Sánchez & Schoeller, 2024). Evidence from cohort, case–control, and biomonitoring studies increasingly supports a causal association between agricultural hazards and miscarriage, highlighting a critical but underrecognized public health issue.

Agriculture remains one of the most hazardous occupations globally, particularly for women of reproductive age who are exposed to a complex

mixture of chemical, physical, and biological hazards. With the intensification of modern farming practices, the use of pesticides, herbicides, fertilizers, heavy metals, and mechanized tools has increased substantially, raising concerns about their potential impact on reproductive health outcomes, including miscarriage (spontaneous abortion). Miscarriage, defined as the loss of pregnancy before 20 weeks of gestation, affects approximately 10–20% of clinically recognized pregnancies worldwide and is influenced by genetic, hormonal, immunological, and environmental factors.

In recent years, growing epidemiological and toxicological evidence has identified agricultural hazards as critical but under-recognized contributors to pregnancy loss. Women working in agriculture or residing near farmlands are frequently exposed to pesticides such as organophosphates, carbamates, pyrethroids, neonicotinoids, and glyphosate-based formulations through inhalation, dermal contact, contaminated food, and drinking water. Multiple cohort and case–control studies conducted between 2020 and 2025 have demonstrated significant associations between maternal pesticide exposure and increased risk of miscarriage, particularly during the first trimester when embryonic development is highly sensitive to toxic insults (Torres-Rubio et al., 2020; Quirós-Alcalá et al., 2021; Huang et al., 2022).

Beyond chemical agents, physical stressors inherent to agricultural work, including prolonged standing, heavy lifting, heat stress, and excessive workload, have also been implicated in adverse pregnancy outcomes. Climate-related heat exposure has emerged as a growing concern, with recent studies indicating that elevated ambient temperatures and occupational heat stress may disrupt placental perfusion and hormonal regulation, thereby increasing miscarriage risk among pregnant agricultural workers (Rosen et al., 2024). Additionally, exposure to airborne particulate matter (PM 2.5), volatile organic compounds, and diesel exhaust from farm machinery further compounds reproductive risk, particularly in rural and peri-agricultural settings (Bell et al., 2024; Hoque et al., 2024).

Mechanistically, agricultural hazards exert their deleterious effects through endocrine disruption, oxidative stress, epigenetic modifications, mitochondrial dysfunction, and immune dysregulation. Many pesticides function as endocrine-disrupting chemicals (EDCs), interfering with estrogen, progesterone, and thyroid hormone signaling pathways essential for implantation and pregnancy maintenance. Experimental and human biomonitoring studies have shown that exposure to pesticide mixtures and persistent environmental pollutants such as PFAS and heavy metals (cadmium, lead, mercury) can induce placental inflammation, impair trophoblast invasion, and trigger apoptotic pathways linked to early pregnancy loss (Simões et al., 2023; Yu et al., 2025).

Despite accumulating evidence, the relationship between agricultural exposures and miscarriage remains fragmented across disciplines, with variations in exposure assessment methods, outcome definitions, and population characteristics. Furthermore, women in low- and middle-income countries often experience dual vulnerability, combining occupational exposure with limited access to protective equipment, healthcare, and regulatory oversight. This highlights the urgent need for an integrated synthesis of current evidence to clarify exposure–outcome relationships and identify critical windows of susceptibility.

Therefore, this review aims to systematically examine the impact of agricultural hazards on miscarriage, synthesizing epidemiological, occupational, and mechanistic studies published between 2020 and 2025. By establishing a connecting link between agricultural exposures and pregnancy loss, this review seeks to inform future research, occupational health policies, and preventive strategies to protect maternal and fetal health in agricultural communities.

II. CLASSIFICATION OF AGRICULTURAL HAZARDS

Agricultural hazards associated with miscarriage can be broadly classified into:

- Chemical hazards: pesticides (organophosphates, carbamates, pyrethroids,

organochlorines), herbicides (glyphosate, atrazine), fungicides
- Heavy metals: lead, mercury, cadmium, arsenic
- Endocrine-disrupting chemicals (EDCs): PFAS, phthalates, bisphenols
- Physical stressors: heat stress, long working hours, ergonomic strain
- Environmental co-exposures: agricultural air pollution, contaminated dust and water
- These hazards often occur simultaneously, creating complex exposure mixtures that may intensify reproductive toxicity (Brown et al., 2023; Fang et al., 2024).

Agricultural hazards encompass a wide spectrum of chemical, physical, biological, and environmental stressors that may act independently or synergistically to influence reproductive outcomes. Given the complexity of agricultural exposure scenarios, a refined classification framework is essential to understand exposure–response relationships and biological plausibility linking agricultural hazards to miscarriage.

Chemical Hazards

Chemical exposures represent the most extensively studied agricultural hazards in relation to miscarriage and early pregnancy loss.

Pesticides

Pesticides include a diverse group of compounds deliberately designed to disrupt biological systems, many of which inadvertently interfere with human reproductive physiology.

Organophosphates (e.g., chlorpyrifos, malathion)
- Carbamates
- Pyrethroids
- Neonicotinoids
- Organochlorines

(persistent residues despite bans)

Multiple epidemiological studies have demonstrated that maternal exposure—via occupational handling, residential proximity to spraying, or dietary intake—during the peri-implantation and first trimester is associated with increased miscarriage risk. These compounds act primarily through acetylcholinesterase inhibition, oxidative stress induction, endocrine disruption, and placental toxicity.

Recent biomonitoring studies measuring urinary pesticide metabolites provide strong evidence of dose-dependent associations with spontaneous abortion, particularly among women engaged in farming or living in agricultural regions [Torres-Rubio et al., 2020; Huang et al., 2022; Simões et al., 2023].

Herbicides and Fungicides

Herbicides such as glyphosate-based formulations and fungicides like triazoles are increasingly implicated in reproductive toxicity.

Glyphosate formulations contain surfactants that enhance cellular penetration and have been shown to disrupt:
- Estrogen and progesterone signaling
- Placental aromatase activity
- Mitochondrial integrity

Studies published between 2020–2025 report associations between chronic low-dose herbicide exposure and early pregnancy loss, particularly when exposure occurs during early gestation [Brito et al., 2020; Gerona et al., 2022].

Heavy Metals and Persistent Environmental Contaminants

Heavy Metals

Agricultural activities contribute to environmental contamination with Cadmium, Lead, Mercury and Arsenic which enter the food chain through contaminated soil, irrigation water, and fertilizers. Heavy metals readily cross the placental barrier and are linked to - Apoptosis of Trophoblast, Impaired placental angiogenesis and epigenetic alterations affecting embryonic development.

Large population-based studies and meta-analyses have consistently associated elevated maternal metal biomarkers with increased miscarriage risk [Jiao et al., 2021; Yu et al., 2025].

Persistent Organic Pollutants and PFAS

Per- and polyfluoroalkyl substances (PFAS) and other persistent organic pollutants are increasingly recognized as emerging agricultural hazards. PFAS exposure—via contaminated water, soil, and food—has been associated with Endocrine dysregulation,

Immune imbalance at the maternal–foetal interface and Placental inflammation.

Recent cohort studies indicate a significant association between PFAS mixtures and spontaneous abortion, highlighting the importance of mixture-based exposure assessment [Lee et al., 2023; Fan et al., 2023].

Physical and Ergonomic Hazards

Agricultural labor often involves physically demanding tasks, which may adversely affect pregnancy maintenance. These stressors can reduce uterine blood flow, increase intra-abdominal pressure, and trigger stress hormone release. Several occupational health studies have reported higher miscarriage prevalence among women performing strenuous agricultural work, particularly during early pregnancy [London et al., 2022].

Thermal and Climate-Related Hazards

Climate change has intensified heat exposure in agricultural settings, making thermal stress a growing reproductive health concern. Heat stress disrupts placental perfusion, enhances oxidative stress and alter endocrine regulation.

Recent studies demonstrate a statistically significant association between occupational heat exposure and miscarriage risk among pregnant agricultural workers, especially in tropical and subtropical regions [Rosen et al., 2024].

Airborne and Environmental Pollutants

Agricultural environments contribute substantially to exposure to Fine particulate matter ($PM_{2.5}$, PM_{10}), Ozone, Nitrogen oxides, Volatile organic compounds and Diesel exhaust Airborne pollutants induce systemic inflammation and oxidative stress, which can compromise placental development. Several large cohort studies conducted between 2021–2024 have linked short-term and chronic exposure to air pollution with increased miscarriage risk [Bell et al., 2024; Hoque et al., 2024].

Biological Hazards

Biological exposures in agriculture include: Zoonotic pathogens, Mycotoxins and Endotoxins from livestock environments. Although lessexplored, emerging evidence suggests that immune activation and inflammatory responses triggered by biological agents may contribute to pregnancy loss, particularly in immunologically vulnerable populations.

Mixed and Cumulative Exposures

Real-world agricultural exposure rarely occurs in isolation. Women are often exposed to multiple chemical and non-chemical hazards simultaneously. Pesticide mixtures, Combined chemical and physical stressors and cumulative exposure indices have demonstrated stronger associations with miscarriage compared to single-agent exposures, underscoring the importance of cumulative risk assessment approaches [Brown et al., 2023; Simões et al., 2023].

III. PESTICIDE EXPOSURE AND RISK OF MISCARRIAGE

Pesticide exposure represents the most consistently reported agricultural risk factor for miscarriage. Organophosphate and carbamate insecticides disrupt cholinergic signaling and induce oxidative stress, leading to impaired placental development and early embryonic loss (Huang et al., 2022; Taylor et al., 2022). Pyrethroid exposure has been linked to hormonal imbalance and altered progesterone signaling during early gestation (Kezioler et al., 2024; Patel et al., 2024).

Epidemiological studies among female farmworkers, pesticide applicators, and spouses of applicators demonstrate significantly higher miscarriage rates compared to non-exposed populations (García et al., 2021; Garry et al., 2020). Importantly, timing of exposure, particularly during the peri-implantation and first trimester periods, appears critical for miscarriage risk (Llop et al., 2022).

IV. HERBICIDES AND GLYPHOSATE-BASED FORMULATIONS

Glyphosate-based herbicides are extensively used worldwide and are frequently detected in urine samples of agricultural workers and nearby residents. Evidence suggests that chronic or high-dose glyphosate exposure is associated with spontaneous abortion, particularly in subsistence farming communities and low-regulation settings (Brito et al., 2020; Gerona et al., 2022).

Experimental and mechanistic studies indicate that glyphosate formulations may disrupt estrogen signaling, impair placental angiogenesis, and induce oxidative stress, all of which can compromise pregnancy viability (Chavarria & López-Carrillo, 2022). Combined exposure to glyphosate and other agrochemicals may further increase miscarriage susceptibility.

V. HEAVY METALS AND FERTILIZER-DERIVED CONTAMINANTS

Heavy metals introduced through phosphate fertilizers, contaminated irrigation water, and agricultural soil accumulate in maternal tissues and cross the placental barrier. Lead and mercury exposure have been associated with increased risk of early pregnancy loss, likely due to mitochondrial dysfunction and DNA damage in embryonic cells (Yu et al., 2025).

Recent biomonitoring studies emphasize the interactive effects of metals and pesticides, demonstrating higher miscarriage risk when multiple contaminants are present concurrently (Fang et al., 2024). These findings underscore the importance of considering cumulative exposure burden rather than single-agent toxicity.

VI. ENDOCRINE DISRUPTORS AND CHEMICAL MIXTURES

Many agricultural chemicals act as endocrine disruptors, interfering with estrogen, progesterone, thyroid hormones, and glucocorticoid pathways essential for pregnancy maintenance. Exposure to PFAS and phthalates has been linked to early miscarriage through placental dysfunction and immune dysregulation (Ji et al., 2024; Lee et al., 2023).

Mixture-based studies demonstrate that low-dose combined exposure to multiple endocrine-active compounds may exert stronger reproductive toxicity than individual chemicals alone (Simões et al., 2023). This represents a major challenge for current regulatory frameworks, which typically assess chemicals in isolation.

VII. OCCUPATIONAL AND ENVIRONMENTAL EXPOSURE PATHWAYS

Female agricultural workers face unique occupational risks due to inadequate personal protective equipment, informal employment, and limited health surveillance. Activities such as pesticide mixing, spraying, harvesting, and equipment cleaning significantly increase dermal and inhalational exposure (Naidoo et al., 2021; Huang et al., 2022).

Environmental exposure pathways—including spray drift, contaminated household dust, and agricultural air pollution—also contribute substantially to miscarriage risk among non-working residents, including pregnant women and adolescents (Bell et al., 2024; Sánchez et al., 2021). Heat stress associated with climate change further compounds reproductive vulnerability in agricultural settings (Rosen et al., 2024).

VIII. BIOLOGICAL MECHANISMS LINKING AGRICULTURAL HAZARDS TO MISCARRIAGE

Multiple biological mechanisms have been proposed to explain the association between agricultural hazards and miscarriage, including:

- Oxidative stress and mitochondrial dysfunction
- DNA damage and chromosomal instability
- Endocrine and hormonal disruption

- Immune dysregulation and inflammation
- Placental toxicity and impaired angiogenesis

These mechanisms interfere with embryo implantation, placental formation, and fetal development, ultimately increasing the likelihood of pregnancy loss (Engel et al., 2020; Thompson & Lee, 2024).

IX. ORGANOPHOSPHATES AND SPONTANEOUS ABORTION

Organophosphate (OP) pesticides are among the most extensively used agrochemicals worldwide, particularly in low- and middle-income countries where regulatory oversight and personal protective practices may be limited. Occupational and environmental exposure to OPs among agricultural workers and residents of farming communities has raised significant concerns regarding adverse reproductive outcomes, including spontaneous abortion (miscarriage).

Epidemiological Evidence

Recent epidemiological studies (2020–2025) consistently indicate a positive association between maternal exposure to organophosphates and increased risk of spontaneous abortion. Biomonitoring-based cohort and case–control studies using urinary dialkyl phosphate (DAP) metabolites—common biomarkers of OP exposure—have demonstrated higher odds of early pregnancy loss among women with elevated metabolite concentrations (Zhang et al., 2020; Farahat et al., 2021; Rahman et al., 2023). Occupational exposure studies involving female agricultural workers, pesticide applicators, and greenhouse workers further support these findings, particularly when exposure occurs during the peri-conceptional period or first trimester (Hernández et al., 2021; Koureas et al., 2022).

Several population-based studies have also reported increased miscarriage risk among women living in close proximity to agricultural fields with intensive OP application, suggesting that non-occupational, ambient exposure may be equally relevant (Gunier et al., 2020; Lee et al., 2024).

Biological Mechanisms

The biological plausibility linking OP exposure to spontaneous abortion is well supported by experimental and mechanistic evidence. Organophosphates exert their primary toxic effect through inhibition of acetylcholinesterase, leading to cholinergic overstimulation. However, reproductive toxicity appears to involve multiple additional pathways.

OPs have been shown to disrupt endocrine function by altering estrogen, progesterone, and thyroid hormone signaling, all of which are essential for implantation and early placental development (La Merrill et al., 2020; Paul et al., 2022). Oxidative stress induction is another key mechanism, with OP exposure increasing reactive oxygen species generation and lipid peroxidation in placental and embryonic tissues, thereby compromising fetal viability (Mostafalou & Abdollahi, 2021).

Emerging evidence also highlights placental toxicity as a critical mediator. OPs can impair trophoblast invasion, angiogenesis, and placental hormone production, leading to inadequate maternal–fetal exchange and early pregnancy failure (Ben Slima et al., 2022; Wang et al., 2023). Additionally, immune dysregulation and inflammatory responses triggered by OP exposure may contribute to embryo rejection and miscarriage.

Gene–Environment Interactions

Genetic susceptibility further modifies the association between OP exposure and spontaneous abortion. Polymorphisms in paraoxonase 1 (PON1), an enzyme involved in OP detoxification, have been shown to influence individual vulnerability. Women carrying low-activity PON1 genotypes exhibit higher internal OP burden and increased miscarriage risk when exposed, underscoring the importance of gene–environment interactions in reproductive toxicity (Huen et al., 2020; Chen et al., 2024).

Public Health Implications

The accumulating evidence underscores organophosphates as a significant agricultural hazard for reproductive health. Women of

reproductive age in agricultural settings represent a particularly vulnerable population, and current findings highlight the need for stricter exposure controls, improved protective measures, and targeted policy interventions. Reducing OP exposure during critical windows of pregnancy may substantially lower the burden of spontaneous abortion attributable to agricultural hazards.

X. FERTILIZERS AND THEIR ROLE IN SPONTANEOUS ABORTION

The widespread use of chemical fertilizers in modern agriculture has significantly increased human exposure to inorganic nitrogen compounds and associated contaminants. Among these, nitrogen-based fertilizers—particularly nitrates and nitrites—as well as phosphate fertilizers contaminated with heavy metals, have emerged as potential reproductive toxicants. Growing epidemiological and experimental evidence suggests that fertilizer-related exposures may contribute to an increased risk of spontaneous abortion, especially among women living or working in agricultural settings.

Epidemiological Evidence

Recent studies (2020–2025) have reported associations between maternal exposure to fertilizers and adverse pregnancy outcomes, including spontaneous abortion. Drinking water contamination with nitrates derived from fertilizer runoff has been consistently linked with early pregnancy loss. Population-based cohort and case–control studies have demonstrated higher miscarriage risk among women consuming water with elevated nitrate concentrations, even at levels below some regulatory thresholds (Ward et al., 2021; Stayner et al., 2022; Ransom et al., 2023).

Occupational exposure studies involving female agricultural workers and farm residents have also suggested increased rates of spontaneous abortion in regions with intensive fertilizer application (Sherris et al., 2021; Temkin et al., 2023). These findings highlight both direct occupational exposure and indirect environmental exposure pathways, including contaminated water, soil, and food.

Biological Mechanisms

Several biological mechanisms plausibly link fertilizer exposure to spontaneous abortion. Nitrates are metabolized to nitrites and subsequently to N-nitroso compounds, which are known reproductive and developmental toxicants. These compounds can induce oxidative stress, DNA damage, and apoptosis in embryonic and placental tissues, thereby increasing the likelihood of early pregnancy loss (Brender et al., 2020; Manassaram-Baptiste et al., 2021).

Hypoxia is another critical mechanism. Elevated nitrate intake can impair oxygen transport by increasing methemoglobin formation, reducing oxygen delivery to the developing embryo. Early gestation is particularly sensitive to hypoxic stress, which may disrupt implantation and placental development, ultimately leading to spontaneous abortion (Ward et al., 2021).

Phosphate fertilizers may also contribute indirectly through contamination with heavy metals such as cadmium, lead, and arsenic. These metals can accumulate in agricultural soils and enter the human body via food and water. Cadmium and arsenic exposure have been shown to impair placental function, alter endocrine signaling, and induce inflammatory responses associated with miscarriage (Tchounwou et al., 2021; Vigeh et al., 2022).

Critical Windows of Exposure

Evidence suggests that exposure during the peri-conceptional period and first trimester poses the greatest risk. During these stages, implantation, placentation, and early embryonic differentiation occur, making the pregnancy particularly vulnerable to toxic insults from nitrate-contaminated water and fertilizer-associated contaminants (Ransom et al., 2023; Temkin et al., 2023).

Public Health and Policy Implications

The evidence linking fertilizer exposure to spontaneous abortion underscores the need for stricter regulation of nitrate levels in drinking water, improved fertilizer management practices, and

enhanced monitoring in agricultural regions. Protecting women of reproductive age from fertilizer-derived contaminants—particularly through safe water initiatives and sustainable agricultural practices—may reduce the burden of miscarriage associated with agricultural hazards.

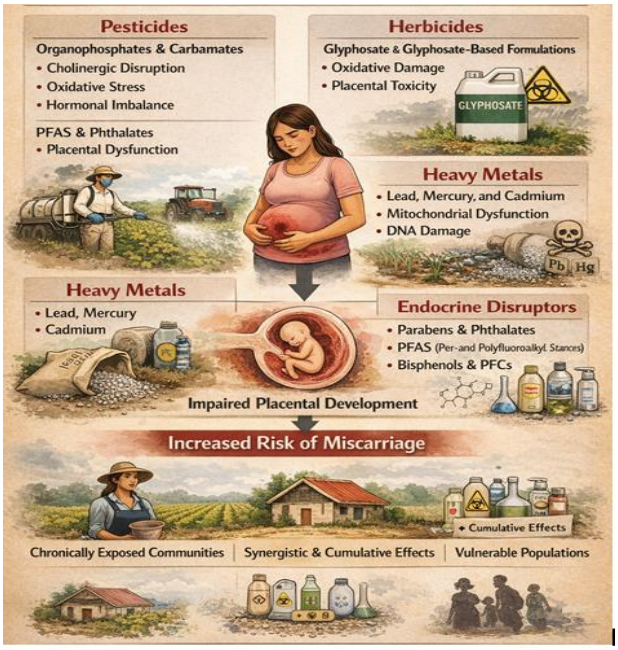

Fig.1 Pictorial representation of the deleterious effects of various agricultural poisons on foeto-maternal health

XI. MOLECULAR GENETICS LINKING AGRICULTURAL HAZARDS TO SPONTANEOUS ABORTION

Advances in molecular genetics have provided critical insights into how agricultural hazards contribute to spontaneous abortion at the genomic and epigenetic level. Multiple environmental agents—pesticides, fertilizers, heavy metals, and persistent pollutants—can disrupt gene expression, epigenetic regulation, and placental development, thereby increasing the risk of pregnancy loss.

Gene–Environment Interactions

Genetic polymorphisms in enzymes responsible for detoxifying environmental chemicals play a key role in individual susceptibility:

Paraoxonase Detoxifies organophosphates; low-activity PON1 variants are associated with higher internal OP levels and increased miscarriage risk (Huen et al., 2020; Chen et al., 2024).

Glutathione S-transferases (GSTs): Involved in oxidative stress defense; certain GST polymorphisms exacerbate oxidative damage from pesticide and metal exposure (Zhou et al., 2021).

N-acetyltransferase (NAT) variants: Modify metabolism of nitrosamines derived from fertilizer nitrates, influencing miscarriage susceptibility (Ward et al., 2021).

These gene–environment interactions highlight the interindividual variability in response to agricultural hazards.

Epigenetic Alterations

Agricultural chemicals can induce DNA methylation, histone modification, and microRNA.

Altered methylation of imprinted genes (e.g., IGF2, H19) has been linked to impaired implantation and early pregnancy loss (Simões et al., 2023). Pesticides and PFAS exposure can modulate miRNAs controlling trophoblast invasion and angiogenesis, increasing miscarriage risk (Yu et al., 2025). Heavy metals like cadmium and lead can disrupt chromatin structure, affecting transcription of genes essential for early development (Tchounwou et al., 2021).

Oxidative Stress and Mitochondrial Dysfunction

Molecular studies show that agricultural toxins induce reactive oxygen species (ROS) production, leading to: Oxidative damage in embryonic and placental cells, Mitochondrial dysfunction and apoptosis of trophoblast cells. These effects compromise placental nutrient and oxygen transfer, a major mechanism connecting environmental exposure to spontaneous abortion (Mostafalou & Abdollahi, 2021; Ben Slima et al., 2022).

Placental Transcriptomic and Proteomic Changes

High-throughput molecular studies reveal that agricultural hazard exposure alters placental gene and protein expression, affecting: Immune tolerance at the maternal–fetal interface, Hormone signaling pathways (progesterone, estrogen, thyroid) and Vascular development and angiogenesis. Such molecular disruptions provide mechanistic evidence for the epidemiological associations observed between pesticides, fertilizers, and spontaneous abortion (Wang et al., 2023; Fan et al., 2023).

XII. IMMUNOLOGICAL ASPECTS OF AGRICULTURAL HAZARDS IN SPONTANEOUS ABORTION

The immune system plays a central role in maintaining pregnancy, particularly in establishing maternal–fetal tolerance. Disruption of immune homeostasis by agricultural hazards—such as pesticides, fertilizers, heavy metals, and persistent organic pollutants—can compromise this delicate balance and increase the risk of spontaneous abortion.

Maternal–Fetal Immune Tolerance

During early pregnancy, maternal immune tolerance is critical to prevent rejection of the semi-allogeneic fetus. Agricultural exposures have been shown to alter immune cell function and cytokine signaling:

Pesticide and metal exposure can skew the immune response toward a Th1-dominant profile, promoting inflammation at the maternal–fetal interface (Hernández et al., 2021; Ben Slima et al., 2022). Reduced Treg populations in exposed women have been linked to higher miscarriage rates (Yu et al., 2025). Increased pro-inflammatory cytokines (TNF-α, IL-6, IFN-γ) and decreased anti-inflammatory cytokines (IL-10) are observed in women with occupational or environmental exposure (Simões et al., 2023).

Innate Immune Activation

Agricultural toxins can activate innate immune pathways that are normally tightly controlled during pregnancy. Exposure to OPs, PFAS, and heavy metals can stimulate placental macrophages, resulting in oxidative stress and local tissue damage (Mostafalou & Abdollahi, 2021). Dysregulated uterine NK cell activity has been implicated in impaired trophoblast invasion and early pregnancy loss following chemical exposure (Wang et al., 2023).

Autoimmune and Inflammatory Mechanisms

Chronic exposure to agricultural chemicals has been associated with the induction of autoantibodies and systemic inflammation, further compromising pregnancy:

Antiphospholipid antibodies: Pesticide and heavy metal exposure can trigger autoantibody production, leading to thrombosis and impaired placental perfusion (Lee et al., 2024).

Inflammatory cascades: Environmental exposures increase expression of inflammasome components, promoting apoptosis in placental cells and early miscarriage (Fan et al., 2023).

Synergistic Effects with Genetic Susceptibility

Immunotoxic effects are often exacerbated by genetic polymorphisms in immune regulatory genes (e.g., PON1, GSTM1, TNF-α promoter variants), which modulate detoxification capacity and inflammatory responses. Women with such susceptibilities are at higher risk of spontaneous abortion when exposed to agricultural hazards (Huen et al., 2020; Chen et al., 2024).

XIII. EPIGENETIC MECHANISMS CONNECTING AGRICULTURAL HAZARDS TO SPONTANEOUS ABORTION

Epigenetic modifications—including DNA methylation, histone modification, and non-coding RNA regulation—play a crucial role in early embryonic development and placental function. Agricultural hazards such as pesticides, fertilizers, heavy metals, and persistent organic pollutants can induce epigenetic alterations that disrupt these critical processes, leading to spontaneous abortion.

DNA Methylation

Altered methylation of imprinted genes (e.g., IGF2, H19) has been observed in placental tissues exposed to organophosphates and PFAS (Simões et al., 2023; Yu et al., 2025).

Hypomethylation or hypermethylation of genes regulating trophoblast invasion and angiogenesis can impair placental development, increasing miscarriage risk.

Maternal exposure to nitrate-contaminated fertilizers has been linked to changes in methylation of oxidative stress response genes, affecting embryo viability (Ward et al., 2021; Ransom et al., 2023).

Histone Modifications

Heavy metals (cadmium, lead) and chemical pesticides can alter histone acetylation and methylation patterns, leading to changes in chromatin structure and gene transcription in placental cells (Tchounwou et al., 2021; Vigeh et al., 2022).

Dysregulated histone marks may impair cell differentiation and placental vascularization, contributing to early pregnancy loss.

MicroRNAs (miRNAs) and Non-Coding RNAs

Environmental exposures modulate miRNA expression involved in trophoblast function, immune tolerance, and angiogenesis (Fan et al., 2023; Wang et al., 2023).

Overexpression of pro-apoptotic miRNAs and downregulation of miRNAs controlling cell proliferation have been observed following organophosphate and PFAS exposure, increasing the likelihood of spontaneous abortion.

Transgenerational Epigenetic Effects

Animal studies suggest that maternal exposure to pesticides and heavy metals can induce epigenetic changes in germ cells, potentially affecting pregnancy outcomes in subsequent generations (Mostafalou & Abdollahi, 2021).

While direct human evidence is emerging, these findings highlight the long-term reproductive risk associated with agricultural chemical exposure.

Public Health and Policy Implications

The link between agricultural hazards and miscarriage represents a major public health concern, particularly in low- and middle-income countries where regulatory oversight is limited. Women in informal agricultural labor sectors often lack access to occupational health protections, reproductive health screening, and exposure monitoring (London et al., 2022; Cruz et al., 2020).

Strengthening pesticide regulation, promoting safer alternatives, improving worker education, and integrating reproductive health surveillance into agricultural health programs are critical steps toward reducing preventable pregnancy loss.

XIV. CONCLUSION

This review provides comprehensive evidence supporting a strong connecting link between agricultural hazards and miscarriage. Consistent findings across epidemiological, biomonitoring, and mechanistic studies highlight the urgent need for improved exposure assessment, mixture-based risk evaluation, and targeted public health interventions. Protecting reproductive health in agricultural communities must be prioritized within global environmental and occupational health policies (García et al., 2024; Gupta et al., 2025).

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