

# Nutritional Impact on Embryo Implantation. Review of the Literature

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## Abstract

The implantation procedure involves a “biofilmic” mechanism of organism protection against threat. Immune-inflammatory procedures expressed by nutritional, molecular and biochemical factors related to homeostasis ensure successful incorporation of blastocyst in the uterine ecology. The feeding chain of the host mother, the embryo and their microbiota modifies the human intrinsic environment, hormone levels, fetal characteristics and growth.

This study was conducted to provide information about the effects of diet on implantation quality in an attempt to therapeutically synchronize the development of blastocyst within the nourishing mothers. The issue is generalized to all “windows of alien implantations”.

The formation of life (: fertilization) and its development is a consequence of biochemical reactions (: mitochondrial cycle, replication, regeneration, oxidation, apoptosis, etc.). Homeostasis is called the body’s ability to keep its internal ecosystem stable despite exogenous changes. The whole process involves energy consumption, operative coordination of various organs, especially between the nervous and endocrine systems.

Instability of homeostasis predisposes to “miscarriages”.

Key elements that enhance acid-base equilibrium, oxygen demands and indirectly implantation success are proteins, trace minerals, vitamins, omega-3 fatty acids, enzymes, fruit and vegetable phytonutrients, probiotics. Restriction of processed or foods polluted with endocrine disrupting chemicals and microbes, sugar, saturated and trans fatty acids prevents genetic deterioration, ageing and troublesome implantations.

Balanced diet, digestion and hormone-dependent metabolism identifies the efficiency of our reproductive system and homeostatic implantation procedure.

**Key words:** Implantation; Nutrition; Diet; Microbiota; Oxidative Stress; Inflammation; Immunity.

## Physiology and Mechanisms of Implantation

The responses to the artificially implanted medical devices are different for each particular material sharing a **common characteristic: induction of the host answer**. This means an inflammatory fibro-vascular encapsulation of the “intruder” so that the foreigner is isolated and does not interact with the “householder”. Water is the main solvent optimizing physicochemical changes of the surface of “biological substance” (: oxidation, **hydrophilia** or **hydrophobicity**, antimicrobial action) modulating the immunity reactions and reducing the negative consequences of implantation. That concept applies to the mother and embryo natural connection. In order for the blastocyst to be incorporated in the surface of the endometrium, it should **collide firmly** and have a feed-back. **Cell surface hydrophobicity and the ability of binding fibronectin, vitronectin and collagen type**

**1** are important for anchoring the implants. The surrounding microenvironment and resources promote the expression of a hydrophilic cell surface which triggers “infections”. Hydrophilia is necessary because the Ca<sup>++</sup>, Na<sup>+</sup> and Cl<sup>-</sup> ions will sit on the water crust. Proteins from the blood and fluids of tissues that have been diffused around the implant are absorbed into the water layer. The protein layers formed are rearranged, changing shape and structure depending on the chemical structure of the surface, the temperature and make up the welding area with the cells. [1, 2]

Water, proteins, carbohydrates and lipids are vital dietary components necessary for organisms. **The immunological system distinguishes** pathogens, separates **useful and familiar proteins from harmful and foreign ones**, detecting “dangerous” signals such as microbes, non-apoptotic, necrotic cell death. Orientation and movement of the fertilized egg, embryo implantation, the formation of a placenta and the embryo-

maternal interactions are mediated by **proteases, cytokines, chemokines which are synthesized by epithelial cells and affect cellular behavior and the outcome of the immune response.** They

Propagate the development of the blastocyst in the uterus, guide it chemotactically and assist its adhesion to the uterine epithelial surface, driving also the decidualization. **Decidual cells also produce those locally active molecules** important for directing and restraining trophoblast invasion and for leukocyte transportation into the decidua until the placenta is established. Stromal cells secrete cytokines that lead the decidualization process and **chemokines that attract leukocytes and help trophoblast migration.** Abnormalities in their production are associated with infertility and miscarriages. [3, 4]

Microbial cells, neoplastic cells etc. exhibit similar actions necessary for their colonization. The presence of complex-type oligosaccharides on the cell surface, **metalloproteases, interstitial collagenase, serine proteases (plasminogen activator)** mediate trophoblast and others invasion. Acid-base ratio (pH), temperatures are important factors for the enzymatic functions. **Coordination of maternal and embryonic processes, transformation of uterus, fetal development and protection** from predators, exchange of nutrients, communications of the embryo and mother, **changes and adaptations via immunity system, the micro-RNA system** are associated with embryo implantation. [5, 6]

**Steps of implantation involve** the recognition and agreement of blastocyst with the endometrium, the violation of the embryo and trophoblast ending in decidualization and placentation. Enzymatic functions and **glycoproteins keep the blastocyst attached to the endometrium.** The hydrophilic nature of glycoproteins allows them to function in the aqueous environment, where they act in cell-cell identification and binding of other molecules. The blastocyst with the mechanism of microvilli migrates inside the endometrium. Then the production of beta-chorionic Synthetic Follicle stimulating hormone begins, while the transformation of the layer cells into decidual cells begins. The complete penetration of the blastocyst into the myometrium takes place gradually while the changes that the cells have undergone in the uterus continue to turn it into a cellular layer which has increased secretion activity. **This “pearl mass” “heals” fully the site of implantation.** [7]

The ability of cytotrophoblastic cells to penetrate depends on many factors.

A. The expression of **surface cell binding molecules.** Cytotrophoblastic (CTB) cells can migrate or differentiate to other cells and merge into forming syncytia, playing key roles in the communication between mother and fetus and in hormone functions. CTB cells multiply and move into the decidua, changing the endometrium and its vessel loops. Uterine factors, oxygen, extracellular matrix, cytokines, growth factors, estradiol, glucocorticoids, human chorionic

gonadotropin hormones regionally present, regulate the cellular transformations, maturation and movement of the trophoblast. [8, 9] CTB cells intrude the endometrium and myometrium using metalloproteinases. Their effect depends on temperature, chemical environment, the interactions with the amino acids of enzymes, electrostatic and hydrophobic forces and hydrogen bonds. [10] Collagen is an abundant protein – “glue” that holds the body, synthesized with the help of **vitamin C. Collagen binding integrins** (transmembrane proteins – receptors) mediate adhesive processes and transmit signals for cellular growth, survival and metastases. When activated, they cause platelet aggregations, fibrosis, neoplasias, restoration of tissues, wound healing and homeostasis. [11,12]

B. The adequacy of the specific **proteases** which deconstruct the extracellular substance, such as **plasminogen activator and metalloproteinases.** Proteases, gelatinases,

C. Proteoglycans are secreted by endometrial mast cells which also mediate inflammation and placental angiogenesis. Overreaction of mast cells may induce immunopathological pregnancy loss. Embryo and tumor or other kind of implantation is regulated by extracellular metalloproteinases. Lower amounts of metalloproteinases are linked with infertility and miscarriages. Expression of plasminogen activator and other matrix enzymes affects apoptosis, proteolysis, angiogenesis, success or failure of the implantation. **Genetic and environmental factors such as diet influence the pH** and indirectly **the enzymatic activities, the defective barriers.** Processed and cooked foods are “dead” because only the natural and raw contain intact nutrients, vitamins, minerals, and enzymes essential for life procedures. [13-15]

D. **Growth factors and cytokines** which further regulate the penetration. **Transformation growth factor, cytokines, estrogen and progesterone hormones, cell adhesion molecules** stimulate penetration, angiogenesis and embryo implantation process. The communication between the immunity cells is accomplished through **cytokines. Cytokines are involved in metabolic disorders maintain homeostasis** between the fetus and the mother and prevent pregnancy loss. [16, 17]

E. **Tissue O<sub>2</sub> levels.** The placenta is the site of oxygen and nutritional exchange between two organizations. Spiral arteries need to be established otherwise fetal malperfusion occurs leading to imbalances between reactive oxygen species and antioxidants, damage to proteins, lipids, DNA and cellular stress. [18]

F. **Microbiome.** The presence of pathogenic **microbiota** in the endometrium competing for food resources and accumulating acidic metabolites in the extracellular space provokes implantation failures. Microorganisms most of the time live in harmony with humans, breaking down foods, producing vitamins and anti-inflammatory substances, strengthening the host immune system and fighting the malignant microbes. Antagonistic behaviors threaten the fertilized egg which might be

eaten by germs. Dietary and life style models affect their quality and quantity. [19]

G. **Acid-base homeostasis.** Ph regulates activation or inactivation of molecules and biofilmformation. The extra -cellular matrix relates to cellular physicochemical features, adherence, detachments, invasions, angiogenesis, migrations, transitions. Clean water, diet rich in fruits, vegetables, seeds and fish sustain alkaline environment. Chaos arises from the excessive growth of pathogenic bacteria and fungi and the subsequent acidification of the body which hinders enzymatic activities. [20-22]

H. **Balanced diet, digestion and hormone-dependent metabolism.** The internal ecosystemdepends on food. Nutrients participate in enzymatic functions, exerting antioxidant and protective activities. The main source of energy is carbohydrates. Dietary lack of proteins and amino acids leads to weak immune system, fluid retention, interstitial edema, infertility and implantation failure. Amino acids are involved as energy sources **for cell repair,survival, regeneration and growth, Krebs cycle, enzymatic functions, metabolism.** [23]

#### Aim and Methodology of Literature Search

A computerized search was performed in pubmed and medline regarding diet and its influence on embryo or other alien implantation. The key words used were: implantation, nutrition, diet, microbiota, oxidative stress, inflammation, immunity.

There were many databases listed e.g. with the combination of words “implantation” and “diet”**984 articles** and **88 reviews** were found and with “implantation” and “nutrition”**936articles, 189 reviews** were written. However comprehensive-systematic-overview reviewarticles, longitudinal, experimental, clinical and comparative studies, meta-analyses were preferred because these documented and clarified the relation of nutrition with implantation procedure.

With the combination of “implantation window” and “diet” there was one experimentalstudy on mice investigating the effects ofintegrin  $\beta 3$  and leukemia-inhibitory factor in theendometrium of controlled ovarian hyper stimulation during the implantation window?

With the words “embryo implantation” and “diet” there were **101 articles, 10 reviews.**

With the words “embryo implantation” and “oxidation” there were **17 articles and onereview.**

With the combination of “embryo implantation” and “oxidation” and “diet”**one article** was published, hypothesizing that diet and its constituents may influence the timing and maintenance of pregnancy.

With the words “embryo implantation” and “inflammation” and “diet”**two review articles** commenced adipokines (leptins) and dietary components influencing reproductive health. Leptin is a hormone secreted by adipose tissue signaling hypothalamus, regulating satiation, immunity, fertility and the nervous system.

With the words “embryo implantation” and “immunity” and “diet” none was noted.

With the words “embryo implantation” and “immunity” and “nutrition”**one meta-analysis** studied the transcriptomic biomarkers of endometrial receptivity, fertility and infertility. It highlights the genetic, inflammatory, immunity pathways involved in pathologies of implantation procedure.

With “embryo implantation” and “microbiota” and “diet”one article referred to dietary interventions, amino acid metabolism, probiotics and prebiotics of intestinal bacteria which are implicated in the development of metabolic syndrome, reproductive performance, health of mother and fetus. The microbiome and metabolism are connected to diet and reproduction.

With the combination of “embryo implantation” and “homeostasis” and “diet”**4 articles** (clinical trial, experimental) referring to impairments produced by toxins and under nutrition were announced. The peri-implantation maternal malnutrition was incriminated for reproductive impairments.

With the word “implantation window” and “oxidative stress” and “nutrition” or “implantation window” and “oxidative stress” and “diet”or “embryo implantation” and “oxidative stress” and “nutrition or diet” none was reported.

#### Factors Affecting Negatively the Implantation Procedure

Disorders of placentar implantation have been associated with in vitro fertilization, the increased use of caesarean section ending to negative outcomes. **Angiogenetic factors,cytokines, growth factors, cell adhesion molecules, hormones regulating angiogenesis andimplantation** are influenced by the feed-food load. The quantity and quality of **carbohydrates** affect glucose and insulin metabolism, obesity, increase in bacterialmetabolites, ovulation, fertility and implantation. [16, 24, 25]

Blastocyst must be inserted without damaging the tissues. “Readability”, retention ability, and biocompatibility are necessary for any implantation site. **Endometrial pathologies suchas abnormal microbial ecosystem, inflammations or trauma relate to desynchronization between** the blastocyst and endometrium and displacement of the implant. **Negative factors** of implantation procedure are **oxidative stresses** that result in hormonal imbalances, mitochondrial abnormalities, the shortening of telomeres in the ovary, dysfunction of granular cells, lipid damage, alterations of proteins and their glycosylation, DNA damage and enzyme dysfunction. Autoimmune diseases, immune intolerance to the fetus, T-helper cells, natural killer cells, chronic inflammatory diseases, hormonal and eating disorders, alcohol, smoking, anxiety, thrombophilia etc. are implicated in failure of fertilization and implantation.[26-30]

**Poor nutrition** leads to the damage of the DNA, lipids and proteins, gestational failures.Intake of micronutrients before and throughout pregnancy prevents reproductive adverse outcomes.

Vitamins and minerals control metabolism, gene expression and prevent imbalances between the production and scavenging of radical oxygen species. Increased copper levels relate to polycystic ovary syndrome, androgen excess, oxidative stress and inflammation. [31-33]

Calcium and zinc influence enzymatic functionalities important for embryo-endometrial interactions. Folate, zinc has antioxidant effects and is important for apoptosis, implantation, placentation, fetal development. [34] **Insufficient intake of trace elements, smoking, anxiety, drugs, environmental pollutants, heavy metals create imbalances**, unexplained infertility and implantation failure. [35] Food pollutants (dioxins, pesticides) are hazardous to cardiovascular, neuroendocrine and other systems. They induce inflammations, oxidative stress, diabetes, various diseases. Human genome is implemented in specific responses against foreign particles and unnatural byproducts.

**Metabolic derivatives from enzymatic or non-enzymatic cleavage of drugs and food** can cause cellular dysfunctions, mutations, toxicity. [36-38]

The endometrium is an endocrine organ which communicates with molecular blastocyst signals and other organs. The uterus produces prostaglandins, cytokines, interleukins, TNF and the placenta produces progesterone. Trophoblast suppresses neutrophils, natural killer cells, and cytokines (: immune tolerance to the embryo). [39]

**Homeostasis** plays an important role in implantation success and is mainly associated with dietary **proteins, trace elements, vitamins, phytonutrients, and omega-3 fatty acids**. Hypothalamus appears to be the center of detection of nutrient levels coming from food intake and eventually coordinates hepatic and pancreatic metabolism, hormone secretions, and control of glucose, fatty acids levels and homeostasis. Nutritional deficits, food intolerances and their related inflammations, metabolic disorders elicit imbalances of the host ecosystem, unsuccessful adaptations of the two coexisting organisms, disturbances of fetal growth and miscarriages. [40, 41]

The intrinsic microbiome regulates the immunity system and fertility factors, affects the microbiota of the embryo and state of health. The **gut microbiome** regulates the estrogenic circulating load through enzymatic releases, participates in metabolic pathways, offering protection from diseases and ideal homeostasis. **Symbiosis** fortifies the immunity system against inflammatory processes. Dysbiosis results in metabolic syndrome, neoplastic, cardiovascular, endometrial diseases and reproductive failures. Avoiding toxins, preference of fermentable fibers, vegetables and fermented food cultivates the benign microbiota and balances various sites of flora. [42-45]

Fetus-endometrial communications and dehiscence are elucidated by chromosomal abnormalities, molecular **pathologies, and metabolic imbalances of the embryos, the mother or both. The uterus and its tissues, the implantation procedure are influenced by environmental factors**. [46, 47] **Unhealthy lifestyles and nutrition interferes**

**with physiological processes causing inflammations, mitochondrial and cellular dysfunction, and endocrine disorders. The mitochondria** generate ATP energy demands for biochemical cycles, anti-oxidant and anti-inflammatory responses and homeostasis. [48, 49] Cellular parameters, stresses and impairments, extracellular matrix are influenced by food intake and dietary deficiencies. Low serum magnesium is related with increased risk of inflammations and death. Vitamin D inadequacy interferes with calcium and bone equilibrium. [50-52] Balanced diet secures the immunity system against disorders, inflammations, deteriorations of cells and tissues. The immunity cells communicate with the gut microbiome which incorporates nutrition and their metabolic byproducts affect host metabolism, physiological processes, infectious status and indirectly implantation window. [53, 54]

### Dietary Factors Affecting Embryo Implantation

**Water is the most important macronutrient of the body.** Dehydration has adverse effects on the integrity of the cell membrane, protein structures and cell viability. Encapsulation of the fertilized egg ensures its protection from enzyme activities, acids, microbes and its survival. [55] Chemicals disrupt phospholipids and membrane proteins causing cellular death.

**The stability of cell wall, membranes and enzymes depend on solvents and aquatic microenvironment.** However industrial poisonous chemicals in water are toxic to plants, animals and humans. Chromium, iron, nickel, copper and zinc induce DNA damage and inhibition of its repair, oxidative stress. Exposure to chlorinated compounds from water supplies demonstrated teratogenic defects, increased resorption sites in maternal rats.

Pregnant women who drink tap water present a higher risk of miscarriage due to **chlorine by-products** used for water purification. [56-58] **Toxins** are also secreted by pathogenic bacteria. Water-soluble toxins pass through the cellular membrane into the cytoplasm by making a channel. [59-64] **Bisphenol-A**, a widely used chemical in the production of plastics, may have estrogenic effects, reducing the size of the implanted pregnancies or ending the pregnancies. General population has been exposed to this substance by diet or water. [65, 66] **Caffeine** contributes to mild dehydration and negative metabolic balance of minerals by higher urine excretion of potassium, sodium, inorganic phosphate, magnesium and calcium. Exposure to caffeine affects uterine receptivity and placenta and can cause epigenetic changes in the developing fetus. [67, 68]

**Diet is associated with low-grade systemic inflammation. Deleterious food proteins** have negative effects on implantation period. **Beneficial plant proteins** promote cell proliferation, differentiation and growth. Green leaves are rich in good proteins, calcium, iron, amino acids and carotenoids. **Phycobiliprotein found in algae** has oxygen free radical scavenging properties and reduces inflammatory mediators protecting tissues and organs. [69- 73]

The **molecules** that are secreted during pregnancy, such as interferon, estrogen, chorionic gonadotropin and progesterone, regulate the expression of genes for nutrient carriers. **Amino acids** are signaling molecules in fertilization and embryonic implantation. The intestinal bacteria metabolize the amino acids and influence their entrance in the circulatory system. Alterations of the gut microbiota and their metastases to uterus results in uterine dysregulation as well as changes in physiologic biochemical pathways of pregnant women and fetal development. Nutrition rich in amino acids, probiotics and prebiotics balance the endometrium, implantation, and placenta and fetus performance. Food supplementation with **arginine** seems to enhance the development of the fetal placenta.[74-75]

Glucose-sites may be implantation sites. **Saccharides** together with polyphenols, alkaloids, and others affect cell implantation, detachment, proliferation and angiogenesis. The endometrial receptivity involves interactions mediated by leptins, integrins, enzymes, proteins, cytokines, growth factors, prostaglandins, angiogenic peptides. **Carbohydrates** play an important role in the interactions between cells and their binding proteins (**leptins**) are expressed in the peri-implantation period. We must eat the good carbohydrates which are rich in omega-3 fatty acids and unsaturated fats and fibers. Grains and legumes include lectins (proteins) which bind to cellular surface and cytoplasm and have specificity for saccharides. Lectins possess antioxidant activity and ability to normalize blood sugar level. [76-80]

Cow's milk and meat contain high concentrations of dioxins, while vegetable milks do not. Lactase is low or absent in adults resulting in insufficient breakdown of lactose. **Lactose** is toxic to the unfertilized egg and may increase infertility and implantation failure.[81-83]

**Metabolism is compromised by hyperglycemia**, leading to defective mineralization and maturation of tissues. Obesity and diabetes result in poor healing, glycation of proteins. Advanced glycation byproducts change the permeability of endothelium and its anti-thrombotic properties, trigger the production of inflammatory cytokines and growth factors, and decrease the local circulation through the expression of adhesion molecules and chemokines. **Hyperglycemia** causes enzymatic dysfunction and glycation of collagen, tissue fragility. Maternal hyperlipidemia predisposes to epigenetic metabolic and fetal disorders.

**Low glycemic food rich in omega-3 and omega-6 fatty acids, vegetable proteins and antioxidants improve fertility.** **High-fat** diet slows the integration of the foreign implant. For example dental implants in patients with uncontrolled type 2 diabetes are hazardous.[84-87]

**Polyunsaturated, long chain, Omega 3** is essential fatty acids which are an integral part of cell membranes throughout the body, thus significantly affecting the function of membrane receptors, the regulation of inflammatory procedures. The **fatty acids of cell membranes seem to serve intercellular communication** in the systemic inflammatory reaction of the body and affect the results of coronary stent or other implantation. **Omega fatty acids protect the mother and fetus from the**

**risk of inflammation**, influencing the implantation of embryos through prostaglandins. Intake of **ω3-Poly Unsaturated Fatty Acids** improves oocyte and embryo quality, the probability of implantation, pregnancy and birth among women undergoing assisted reproduction. However, harmful industrial chemicals that accumulate in food rich in omega fatty acids (fish etc.) can have negative effects.[88-93]

The **consumption of essential fatty acids** from plant sources promotes fertility, embryo implantation and protection, placenta function and regulates hormonal balance. **Fats from animal sources, as well as cooked fats, negatively affect the function of the cell membrane**, causing an excess of estrogens. **The consumption of foods rich in unsaturated fatty acids enhances implantation**, since it increases the body's sensitivity to insulin and minimizes inflammation. Females wishing to have a child should consume a moderate amount of monounsaturated and polyunsaturated fatty acids, in particular omega-3 fatty acids. **Saturated fats have been accused of increasing blood cholesterol** and the risk of **developing diseases** such as cardiovascular disease. Olive oil has anti-oxidant substances. When oil is heated at high temperatures it is altered and converted into a trans form, being foreign to cell membranes and reproductive organs. **Trans fatty acids** are found in all fried and processed foods. **Trans fatty acids** activate or disable the function of cells, affect the process of inflammation, ovulation, infertility. [94-95]

**Micronutrients** are essential in a variety of biological processes including effective immune-responses, diminishing inflammations and oxidative stress. **Deficiencies in trace elements are correlated with** autoimmunity disorders, systemic inflammation and repeated implantation failure. [96-97]

**Ions** and growth factors cause chemotactic effects. **Calcium** induces proliferation of cells into the implants. Calcium-binding proteins play important roles in embryo implantation success and endometrial receptivity. Vitamin D and calcium deficiencies are common and have a significant impact on growth and development. Calcium is more effective from food than supplements. [98-100] **Magnesium** supports all tissues and immunity system, influences various physiological processes such as differentiation of mesenchymal stromal/stem cells. It acts beneficially on the macrophage polarization having a protective effect by decreasing cytokine production involved in the tissue healing and the possible failure of the implants. Decrease of serum magnesium has a negative impact on bone metabolism and tissue around implants. Magnesium-based biomaterials can induce a faster inflammation resolution while improving tissue repair. [101-103]

**Vitamin D** relates to maternal immunity system, influencing the balance between pro and anti-angiogenic factors and the process of placenta angiogenesis. Dietary supplementation with vitamin D balances the ratio of maternal T-helper 1 and 2 cells and cytokines. Its deficiency is associated with implantation failures and pregnancy complications.[104-105]

**Pesticides, fertilizers, hormones present in food can interfere with human endocrine system and cause liver**

**congestion.** Basic function of the liver is the processing of hormones and production of bile. Bile is excreted by the liver for digestion and absorption of indigestible fats and fat soluble vitamins and hormones. **If bile does not flow, difficulties eliminating excess estrogen exist. Beetroot and apples help decongestion of bile.** Apples and apple products are a source of polyphenols, fibers, carotenoids and other nutrients. Polyphenols fight obesity by scavenging free radicals, regulating signaling and transduction pathways in cells and tissues, especially adipose. They reduce body fat and body mass index and indirectly prevent metabolic diseases. Apples/pears, citrus fruits, green leafy vegetables/salads and cruciferous vegetables consumption is inversely associated with inflammatory vascular diseases and its subsequent malnourishment. [97,106]

Humans are exposed to **hormone compounds derived from animal products or to chemical compounds that disrupt the endocrine system** through food, drug treatments and the environment. Hormones have been used in animal food and their metabolites accumulate in tissues causing toxicity, cancer, endometriosis, infertility and implantation failure. Eggs contribute more to **dietary intake of estradiol** than beef. 17 $\beta$ -estradiol enters the organism through food causing harm to endogenous endocrine system. Estrogen "secretions" from males can mediate the interruptions of the pregnancy of females in which fertilized eggs were implanted. [107-110]

Homeostasis of the uterus and embryo is related to hormones, cytokines and apoptosis all interplaying with nutritional feedback. The quality of food intake can cause abnormalities and maintain inflammation. Dietary products possess **antigenic and microbial load** interacting with the consumer's ecosystem, causing intolerances. **Food intolerances** promote systemic inflammatory diseases including metabolic, cardiovascular and immunity disorders, affecting indirectly the implantation procedure. [111, 112] Tissue integration as assessed with prosthetic implants depends on **local hygiene and "aseptic" nutrition.** Infection of the bowel and neighboring ovaries with gram negative bacteria influences hormonal receptors during the peri-implantation period, provoking embryonic disintegration. [113-115]

**Edible products may possess microbes, affecting the sterilization status of pregnant females and their implants. Microorganisms** are used in food industry for several demands, having also undesirable traits. *Listeria monocytogenes*, *Escherichia coli*, lactic acid bacteria, *Pseudomonas* spp., *Staphylococcus* spp., *Bacillus cereus* etc. observed in market samples affected the phenolic content and antioxidant activity of the food. When digested they are circulating producing systemic inflammatory diseases. [116-118]

Microbes are inserted in the body by direct contact and indirectly by food. Infections predispose to the appearance of metabolic syndrome and its negative effects on implantation and fertility. Microorganisms eat the food of the hosts and their implants. Diet affects the microbial load, the balance between friendly and hostile microbes, the immunity defenses, the inflammatory factors, metabolic dysfunction and insulin of the

consumers. One particular microorganism in food is mycoplasma which is also encountered in gynecological infections. Mycoplasma triggers immune responses and inflammatory disorders in the host including endometritis, reproductive and implantation failures. Its species are detected in serum, milk, sheep, goats, poultry, calves, sea mammals. **Other malignant microbes** detected in chronic asymptomatic endometritis such as *Chlamydia trachomatis* etc. cause infertility, troublesome implantation or miscarriage. Curing the local and systemic pathologies assist infertile women to proceed to successful implantation. [119-124]

There are differences of **intestinal microflora** among individuals. Their activities are responsible for various metabolic, hormonal and immunological processes. Phyto-estrogen (mainly present in legumes and soy products) metabolism and activity depend on intrinsic microbiome. Intake of prebiotics and increase in gut communities of *Bifidobacterium* and *Lactobacillus* promotes health. Diverse imbalances or variations of microbial species result to disorders of the mother and fetus. **Obesity, diabetes mellitus** are associated to the amount of food intake, inflammation and **gut microbiota.** Short chain fatty acids and other metabolites produced by the microbial communities influence insulin signaling and other biochemical cycles. Type 2 diabetes mellitus causes chronic inflammation and affects the immune system, ovulation, implantation, pregnancy, infertility. It relates to inflammatory cytokines and immune-endocrine bidirectional communications. Inflammatory agents interfere with the immune-endocrine interactions between endometrium, myometrium and blastocyst, trophoblast and decidua during pregnancy. [125-127]

Infections, enteric dysfunction, endogenous inflammation associated with adiposity and nutrient deficits influence growth and block the cell cycle progression. **Dietary constituents act as anti-inflammatory and anti-oxidant agents.** When cells dysfunction, they stop proliferating and secrete inflammatory molecules, reactive oxygen species and extracellular harmful components. Polyphenols (rich in fruits and vegetables) promote mitochondrial function and autophagy, reduce oxidative stress, inflammation and cellular senescence (favor to implantation). [128,129]

## Discussion

Understanding the mechanisms by which diet regulates the cell signaling pathways, oxygenation and pH in the uterine environment is important to succeed implantation.

**Implantation depends on inflammatory procedures and cellular stress.** Pregnancy and its preservation include signaling between fetal membranes and mother. Nourishment depends on absorption and circulation. Diabetics, obese women are at risk for inflammations, ischemia, under-nourishment and problems with implantation. [3, 6, 10, 25, 28, 31, 35]

**The implants search useful nutrients and a shelter source.**

**Macro and micro-nutrients** are necessary for the prevention and treatment of diseases, including infertility. **Fortification**

**and supplementation of nutrition prevent illnesses and implantation problems.** Vitamins, trace elements, minerals, omega-3 fatty acids, probiotics and prebiotics strengthen the body. Dietary deficiencies end up to dysfunctions of biological processes and implantation failure. [31-35, 51, 52, 96, 105]

**Adequate hydration** is advised because water constitutes cells, detoxifies the blood, assists circulation, oxygen and nutrient transportation, increases metabolism. **Water** treats hormonal imbalances and female cervical mucus. However water, plants and animals can be contaminated with pathogens or chemicals. Nutrition, water and associated contaminants affect intrauterine installation of fertilized eggs, particularly sensitive to the levels of natural estrogens. **Caffeine intake** antagonizes minerals, dehydrates and augments inflammations. [67, 68]

Hypothalamus regulates metabolism of **energy sources (carbohydrates, fats, proteins) and homeostasis.** **Energy demands are increased during pregnancy.** Failure of parental homeostasis equals to failure of implantation. [41, 48]

The body needs **proteins in large quantities** because they are essential for the synthesis of enzymes, hormones and other chemicals and are involved in the development of tissues and organs. Plant proteins, compared to animal, are associated with a lower risk of developing inflammatory diseases such as diabetes. The epithelial cells of the uterus secrete and/or carry a wide range of molecules, serine, methionine, arginine, lysine, histidine etc. transported through the vessels of the placenta to support conceptus growth. [23, 74, 75, 99]

Fish, grains, vegetables, fruits are the main sources of good carbohydrates. Pasteurized milk does not include enzymes. Lactose is broken down in the intestine into glucose and galactose. Most adults lack lactase to metabolize this milk carbohydrate and therefore it might be toxic to implantation period. Improper glycemic control influences the survival rate of implants. [83, 111, 112]

**Trans-fatty acids, high carbohydrate and animal protein** intake prejudices fertility. **Saturated Trans fatty acids** disable cellular membranes and implantation. A restriction is needed on the consumption of white sugars (exhaust enzymes), **white flour, salt** (hinders enzymes), **saturated and Trans fatty acids** because they accelerate cell aging, the deterioration of genetic material and then implantation failures are favored. [93-95, 109]

**Omega-3 fatty acids** found in fish, olive oil and grains are responsible for various cellular functions, the development of the egg, healthy embryo development. Human body does not produce Omega 3 fatty acids, so these need to be recruited from food. Consumption of 2-3 portions of fish on a weekly basis, is sufficient to have the protection shield of omega 3 fatty acids. [88, 89]

**Food causes disorders of blood-feeding circulation and affects the homeostasis** of the mother and fetus. Important factors are the maintenance of a constant amount of oxygen and carbon dioxide, body temperature, blood acidity, the concentration of salts (Na<sup>+</sup>, Cl<sup>-</sup> ions) and glucose of the body. The whole process requires energy consumption and coordination of

various organs. [111]

**Safe implantation procedure depends on a healthy circulatory system and nourishment supplies.** Sugar and its derivatives have negative effects on implantation because they cause hyperglycemia and then stimulate the release of a large amount of insulin, ending in hormonal imbalance. Eating foods with a low glycemic index is beneficial having anti-inflammatory effect. Such foods are - apples - green vegetables - olive oil - eggs - nuts - fish - seeds - berries. Globally, countries are working towards the healthy diet intake to prevent obesity and risk factors of maternal and infant diseases. [25, 31, 35]

**Fruits and vegetables** are sources of antioxidant vitamins (A, C, E) and antioxidants (lycopene, beta-carotene etc.), trace elements, nutrients (folic acid etc.) essential for health and reproduction. Antioxidants neutralize free radicals that negatively affect the maturation of the eggs, their chances of fertilization, the correct implantation and development of the fetus. These substances are thermo-sensitive and therefore fruits and vegetables should be consumed fresh and raw. **Fibers** help the body to get rid of the excess estrogen and foreign hormones, while maintaining the proper functioning of the digestive system. In addition, they have the ability to maintain blood glucose levels at normal levels. Foods rich in fiber are fruits, dark green leafy vegetables and whole grains. **Implantation is influenced** by molecular mechanisms that depend **on the nutritional elements**, inflammatory agents, genes, sufficient sleep and its influence on hormones. All **vegetables** contain indole-3 carbinol, which is a powerful hormone balancer. Food components such as phenolics in olive oil, fruits and vegetables, yoghurt, legumes, fish, peanuts etc. have therapeutic results. [107, 126, 129]

Studies are exploring the mechanisms by which **food related microorganisms** act, including metabolic pathways, physiology and fermentation that ultimately change the microbial communities. Their characteristics are discovered in order to prevent diseases. It is recommended that food consumption comes mainly from vegetables and fruits rather than animal sources since increased chance of contracting mycoplasma and other pathogenic species is possible. Nutrition modifies microenvironment and cellular hygiene. Gut microbiota depends on quality and quantity of food intake and interacts with the host. **Implantation and gestation depend on food and microbiome.** Women who had many lactobacilli had successful in vitro and in vivo fertilization. It is known that the intrinsic microbiota, the brain and gut communicate and modulate neural, hormonal and immunological pathways. [45, 125, 127]

**Oxidative stress** results in hormonal imbalance, mitochondrial and DNA abnormalities, ageing of the ovary, dysfunction of cells, lipid damage, protein glycosylation and enzyme dysfunction. Food intolerances promote inflammatory cycles interfering with homeostasis and implantation. At a molecular level the food interacts with the genome/gene expression and is implicated in hormonal or metabolic disorders, the body's homeostasis. Embryo and uterus are targets of estrogens and their metabolites. Dietary phytoestrogens influence native estrogen actions in the uterus

during implantation. The preparation of the female body in both physical and assisted fertilization is important for the reduction of miscarriages. Couples, several months before the onset of efforts, should modify their eating habits, alcohol and caffeine abuse, smoking, treat various hormonal disorders, infections, exposure to toxins, diabetes, thyroid diseases, polycystic ovary syndrome.[40, 41, 85]

Diet seems to affect all implants whether they are in uterus (embryo), in the atheromatic plaque (stents, microbes), artificial dental /orthopedic/cardiological, neoplastic or others.

**The implantation is an immune-inflammatory procedure which is influenced by nutritional, molecular and biochemical factors related to homeostasis.**[1, 2, 10, 14, 29, 39, 41, 53, 70, 80, 84, 86,101]

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## Author contributions

Angeliki Tsantsaridou had the idea and wrote this article. George Valsamakis super revised this article. Olga Tsantsaridou, Spyros Potamianos and Sophia Kalantaridou also revised the article. Maria Asprogianni helped with the search of the literature.

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