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Physiological challenges and metabolic adaptations during human fetal development and at delivery

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Summary

Demographic shifts driven by both social and biological factors underscore the need to improve pregnancy care and early childhood interventions to achieve lasting health benefits. From implantation to birth, tightly coordinated physiological and metabolic processes in embryonic and fetal development, coupled with maternal–fetal nutrient exchange, ensure that oxygen supply meets the energy demands of the growing fetus. Critical mechanisms include the higher oxygen affinity of fetal hemoglobin, which facilitates maternal-to-fetal oxygen transfer; endocrine regulators such as human chorionic gonadotropin, which promote placental development; and hypoxia-inducible factors, which support adaptation to low oxygen availability by enhancing glucose utilization, shaping oxygen and lactate metabolism, and contributing to implantation and immune modulation. Additional adaptations—such as shifts in fetal temperature, blood flow, and pH relative to the mother—further optimize oxygen release from fetal blood to tissues. At birth, the neonate undergoes profound respiratory, cardiovascular, and metabolic transitions required for survival in the extrauterine environment. In this review, we examine the central physiological and metabolic mechanisms that enable human embryos and fetuses to grow and survive under these developmental constraints and through delivery.

We further discuss how perinatal metabolic adaptations not only secure immediate survival but also influence lifelong health trajectories, including susceptibility to chronic non-communicable diseases influenced by epigenetics factors. A deeper understanding of these processes may guide interventions aimed at optimizing fetal development, improving pregnancy outcomes, and promoting long-term human health.

1. Social dynamics and contemporary trends in human reproduction

The concept of 'Demographic transition' describes the shift from high birth and death rates in pre-industrial societies to lower rates in modernized ones. In pre-modern societies, fertility was moderated by practices such as late marriage and prolonged breastfeeding, remaining below its biological maximum, while the adoption of contraception played a pivotal role in reducing fertility during the transition (Coale 1984). With modernization, the expansion of reproductive rights consistently contributed to declines in both fertility and mortality, reinforcing social and economic progress (Kollodge 2018). However, population dynamics are also shaped by broader health and environmental challenges, including the resurgence of infectious diseases driven by climatic changes (El-Sayed, Kamel 2020) and the growing threat of antibiotic resistance, which alters microbial ecology and heightens public health risks (Baquero 2021).

Long-term health depends heavily on a well-sustained pregnancy and a well-nourished early childhood, nurtured in a healthy environment and shaped by beneficial habits. The Developmental Origins of Health and Disease (DOHaD) hypothesis highlights the period from preconception through the first two years of life as crucial in shaping long-term health outcomes. Exposure to environmental adversities during this period can negatively influence the development of organs and tissues, increasing the risk of disorders such as obesity, diabetes, hypertension, and cancer later in life (Lyerly et al 2007; McKerracher 2019). Additional factors, such as late pregnancies, are associated with increased risks, including prematurity, multiple births (e.g., twins), congenital malformations, and a higher likelihood of hereditary diseases (Schure et al 2012; Shechter-Maor 2020).

The present review examines the physiological and metabolic challenges that human embryos and fetuses face from zygote attachment to childbirth. We highlight how environmental challenges influence nutrient preferences, fetal oxygen delivery, and the physiological, endocrinological, and metabolic adaptations required for optimal development. Early interventions targeting these adaptations can reduce the risk of chronic diseases later in life while improving immediate pregnancy outcomes and promoting long-term health for both mother and child (Bhutta et al 2013; Marshall et al 2022).

2. General aspects of human ontogeny: fertilization and early steps of development

2.1. The oocyte pathway from the ovary to the uterus

Each month, several follicles begin to mature, but typically only one oocyte is ovulated. It is surrounded by the zona pellucida, a glycoprotein layer that regulates sperm entry. After ovulation, the oocyte is transported through the Fallopian tube by coordinated ciliary motion and tubal fluid dynamics (Atwood, Vadakkadath Meethal 2016). Cumulus cells surrounding the zona pellucida provide key metabolic substrates—such as lactate and pyruvate—to support oocyte energy demands (Huang, Wells 2010). In humans, fertilization typically occurs in the ampulla region of the Fallopian tube , and within ~12–20 h post-ovulation and sperm entry, the zygote forms with male and female pronuclei, restoring diploidy (46 chromosomes) from the haploid gametes (23 chromosomes each) (Balakier et al 1993; Bastawros 2023).

Bathed in nutritive and protective tubal fluids (Aguilar, Reyley 2005), the zygote is gradually transported toward the uterus over approximately 80 hours, a process driven primarily by coordinated ciliary movement and smooth muscle activity (Croxatto 2002). During this journey, the embryo undergoes sequential cleavages: it first reaches the 8-cell compacted stage, then the 16-cell morula, and subsequently progresses to the blastocyst stage (Rossant, Tam 2009).

During blastocyst formation, outer cells polarize to form the trophectoderm, which interacts with the endometrium, while inner cells originate the pluripotent inner cell mass (Leung et al 2016). In the subsequent phase of gastrulation, the inner cell mass differentiates into epiblast and primitive endoderm (Solnica-Krezel, Sepich 2012). The epiblast generates the three primary germ layers—ectoderm, mesoderm, and endoderm—that ultimately give rise to all tissues and organs (Kidder 2020). The trophectoderm further differentiates into trophoblast lineages that mediate implantation, vascular remodeling, nutrient exchange, and hormone production, initiating placentation (Hamilton, Boyd 1960; Turco et al 2018; Varberg, Soares 2021). These early developmental events reflect a highly coordinated interplay of cellular structure, metabolism, and signaling essential for successful implantation and embryogenesis.

2.2. The maternal-fetal interface: implantation, trophoblast function, and immune adaptation

By days 6–7 after fertilization, the blastocyst implants into the uterine lining, where outer trophoblast cells at the polar region proliferate into cytotrophoblasts that fuse to form the multinucleated syncytiotrophoblast. This invasive layer penetrates the endometrial stroma and is essential for placental development, mediating the maternal–fetal exchange of gases, nutrients, and waste products within the placental villi (Hamilton, Boyd 1960; Bischof, Irminger-Finger 2005; Turco et al 2018). Endometrial receptivity, which peaks around days 5–7 after ovulation under the

influence of ovarian hormones, facilitates this process. The trophectoderm differentiates into cytotrophoblasts and syncytiotrophoblasts, and by 9–12 days these structures establish connections with maternal blood vessels. Cytotrophoblasts give rise to villi containing fetal vessels, while cytotrophoblasts differentiate and contribute to extravillous trophoblasts that remodel maternal vasculature, enhancing nutrient exchange and hormone secretion. Human chorionic gonadotropin plays a central role in blastocyst–endometrium interactions, while interleukins regulate signaling both at the uterine lining and at the feto–maternal interface (Castro-Rendón et al 2006; Afshar 2007; Atwood, Vadakkadath Meethal 2016; Vilotić et al 2022). During embryogenesis and organogenesis, the embryo initially relies on histotrophic nutrition from endometrial glands rather than maternal blood, which promotes trophoblast proliferation and differentiation. This increases exposure to key hormones—including estrogen, progesterone, and prolactin—that are essential for sustaining pregnancy and supporting fetal development (Halasz, Szekeres-Bartho 2013; d'Hauterive et al 2022).

Successful blastocyst implantation requires the coordinated expression of specific proteins in both embryonic and endometrial cells. Matrix metalloproteinases 2 and 9 degrade the endometrial extracellular matrix, enabling trophoblast invasion and deeper implantation, while integrins, particularly αvβ1 and αvβ3, support blastocyst adhesion through interactions with ligands such as osteopontin. Human chorionic gonadotropin, secreted by the blastocyst from the earliest stages, signals the corpus luteum to sustain progesterone secretion and exerts pleiotropic immunomodulatory and angiogenic effects essential for implantation and early pregnancy (Kang et al 2014; Ramu et al 2017; Gridelet et al 2020). Compared with cleavage-stage embryos, human blastocysts consume nearly tenfold more glucose, producing high levels of lactate and H^+ ions that acidify the peri-implantation microenvironment. This metabolic reprogramming, far from being a by-product, is a functional adaptation that promotes tissue remodeling, angiogenesis, and maternal–fetal dialogue (Gardner, Harvey 2015; Gurner, Gardner 2025).

Interleukins-1β, 6, and 8 enhance communication between the blastocyst and the endometrium, improving endometrial receptivity and immune adaptation. From the endometrial side, Intercellular Adhesion Molecule 1 interacts with integrins on the trophectoderm to support blastocyst attachment (Massimiani et al 2020). Although maternal tolerance of the semi-allogeneic fetus remains incompletely understood, progesterone by progesterone-induced blocking factor and human chorionic gonadotropin signaling modulate maternal immune cells' function to create a permissive environment for fetal development, promoting tolerance mechanisms (Szekeres-Bartho et al 1997; Nair et al, 2017). These endocrine factors establish and maintain immune tolerance in pregnancy by suppressing harmful maternal alloresponses, limiting antigen presentation, inhibiting NK, T, and B cells, sustaining tolerogenic dendritic cells, inducing regulatory T cells, and recruiting mast cells and regulatory T cells to the fetus–maternal interface (Schumacher et al 2014).

Maternal immune adaptation during pregnancy progresses through three functionally distinct phases. The initial pro-inflammatory state at the maternal–fetal interface promotes implantation and placental development. This is followed by a sustained anti-inflammatory milieu that supports fetal growth and differentiation throughout mid-gestation. In late pregnancy, a re-establishment of pro-inflammatory conditions prepares the maternal–fetal unit for parturition, facilitating the onset of labor and delivery (Mor 2022). Human leukocyte antigen G induces immune tolerance during pregnancy by inhibiting the activity of maternal immune cells, including CD4-positive and CD8-positive T cells, natural killer cells, macrophages, and dendritic cells, thereby preventing fetal rejection. Its dysregulation is linked to complications such as fetal loss (Zhuang et al 2021).

The implantation relies on a receptive endometrium, a competent blastocyst, and coordinated maternal–fetal crosstalk, followed by immune tolerance. Progesterone-induced blocking and chorionic gonadotropin modulate maternal immune cells, promoting tolerance and angiogenesis. Single-cell transcriptomics identifies distinct trophoblast populations contributing to angiogenic pathways. As the first embryo-derived signal, chorionic gonadotropin enhances trophoblast tolerance, boosts uterine NK cells, induces apoptosis via Fas/Fas-Ligand, modulates Th1/Th2 balance and complement factors, recruits regulatory T cells, and drives endometrial angiogenesis through luteinizing hormone / chorionic gonadotropin receptors (Szekeres-Bartho et al 1997; Tsampalas et al 2010). Human leukocyte antigen G induces immune tolerance during pregnancy by inhibiting the activity of maternal immune cells, including CD4-positive and CD8-positive T cells, natural killer cells, macrophages, and dendritic cells, thereby preventing fetal rejection. Its dysregulation is linked to complications such as fetal loss (Barbaro et al 2023). The implantation and placental development rely on tightly regulated trophoblast differentiation, metabolic shifts, and immune modulation to establish a receptive maternal–fetal interface and to sustain early pregnancy.

2.3. From gastrulation to circulation: embryonic and placental development in early gestation.

After implantation, gastrulation organizes germ layers through four evolutionarily conserved morphogenetic movements: emboly (internalization), epiboly (spreading), convergence (narrowing), and extension (elongation). These events are regulated by actomyosin-driven cytoskeletal dynamics and achieved through coordinated cell behaviors, including adhesion, chemotaxis, chemokinesis, and planar polarity, all integrated with embryonic polarity cues and signaling gradients (Solnica-Krezel, Sepich 2012).

The formation of placental villi is a progressive process driven by trophoblast differentiation and maternal–fetal interactions. Cytotrophoblasts give rise to primary villi, which later acquire extraembryonic mesoderm to form secondary villi, and subsequently develop vascularized tertiary villi, establishing the basis for fetoplacental circulation that sustains fetal growth (Gauster et al 2022; James et al 2022).

The separation of maternal and fetal blood circulations was first demonstrated through pioneering experiments, such as injecting colored molten wax into the placenta and uterus (Falkiner 1939). Eighty years later, magnetic resonance studies confirmed the separation of maternal and fetal circulations and enabled the quantification of histologically relevant structural parameters, including the relative proportions of vascular spaces (Melbourne et al 2019). These findings resolved a longstanding debate on maternal-fetal blood flow and significantly advanced the understanding of placental physiology in fetal development (Jensen, Chernyavsky 2019). Beyond nutrient transfer, the placenta also shields the fetus from specific maternal and environmental stressors. The placenta also plays a crucial role in gas exchange, hormone regulation, immune defense, and detoxification. These functions are especially important during the second and third trimesters, when fetal growth accelerates, and body weight typically triples by full term (Burton 2009; Bronson, Bale 2016). Coordinated morphogenetic movements and placental specialization establish the foundations for fetal development, ensuring efficient exchange, protection, and growth throughout gestation.

3. Hormonal regulation during embryo and fetal development

3.1. Hypothalamic-Pituitary-Gonadal Axis and Early Hormonal Regulation

Gonadotropic hormones, secreted by the pituitary gland, regulate testicular and ovarian functions. Their secretion is influenced by neurohormones like norepinephrine, serotonin, corticotropin-releasing hormone, and opioids, which modulate gonadotropin-releasing hormone. Gonadotropin-releasing hormone stimulates luteinizing hormone and follicle-stimulating hormone release, promoting estrogen and progesterone production essential for the menstrual cycle and reproduction (Schally et al 1971; Spergel 2019). Estrogen drives endometrial proliferation, enhancing rough endoplasmic reticulum. Early secretion shows glycogen buildup, nuclear channel systems, and giant mitochondria, marking post-ovulatory changes (Cornille et al 1985).

The coordinated actions of pituitary and placental hormones regulate gametogenesis, endometrial preparation, vascular adaptation, and embryo implantation, ensuring the hormonal environment required for the initiation and support of early pregnancy.

3.2. Maternal hormones support implantation and trophoblast invasion

Maternal hormones and signaling molecules—including corticotropin-releasing factor receptor 1, activin, gonadotropin-releasing hormone 1, human chorionic gonadotropin, prolactin, placental lactogen, estrogens, progesterone, leptin, growth hormone, serotonin, melatonin, and oxytocin—play key roles in regulating energy homeostasis, human chorionic gonadotropin, prolactin, production, and blastocyst development. These factors collectively promote trophoblast attachment, endometrial invasion, and intrauterine remodeling, thereby ensuring a controlled implantation

process. After fertilization, progesterone promotes angiogenesis, preparing the endometrium for implantation. Human chorionic gonadotropin raises prostaglandin E2 in fallopian tubes, influencing estrogen receptor α and β expression. Elevated estrogen lowers uterine vascular resistance via estrogen receptors and activates nitric oxide production which is essential for ovulation, fertilization, implantation, and fallopian tube motility (Atwood, Vadakkadath Meethal 2016; Niringiyumukiza et al 2018; Armistead et al 2020). Maternal hormones and signaling molecules contribute to the regulation of implantation by modulating trophoblast function, endometrial receptivity, and intrauterine remodeling, thereby creating a supportive environment for early embryonic development.

3.3. Insulin and placental growth hormone in maternal-fetal metabolism

Prenatal β-cell development in humans begins around gestational week 9, following the earlier appearance of glucagon-expressing cells at week 8, but not associated to fetal insulin control (Meier et al 2010). The full functional secretion and mature glucose sensing develop later in pregnancy. The placenta, rich in different regulators receptors on syncytiotrophoblasts, is highly responsive to maternal insulin and facilitates nutrient uptake. The maternal glucose levels and placental transfer remain the primary determinants of fetal glucose homeostasis throughout the entire pregnancy (Lager, Powell 2012).

After placentation, placental growth hormone levels steadily rise, exerting effects similar to maternal growth hormone, though with lower potency (Freemark 2010). Placental growth hormone, detectable by mid-gestation, exerts somatotropic actions on maternal liver and adipose tissues. Placental growth hormone promotes gluconeogenesis—the generation of glucose from non-carbohydrate substrates such as amino acids, lactate, and glycerol—and stimulates lipolysis, which releases free fatty acids as an alternative energy source for the mother. These combined effects increase maternal insulin resistance and shift maternal metabolism toward fat utilization, sparing glucose for continuous fetal supply, especially during periods of maternal fasting. As placental growth hormone is produced exclusively by the placenta, its levels drop sharply after birth (Armistead et al 2020; Lain, Catalano 2007; Velegrakis et al 2017). Maternal insulin production also rises gradually to counter placental growth hormone and progesterone-induced insulin resistance, with placental glucose transporter type 1 upregulation enhancing fetal glucose transport (Freemark 2010; Joshi et al 2022). The dynamic interplay between placental hormones, maternal insulin sensitivity, and fetal insulin production ensures adequate glucose availability and metabolic adaptation to support fetal growth throughout gestation.

3.4. Insulin-like growth factors and regulation of fetal growth

Insulin-like growth factors (IGF-1 and IGF-2), insulin-like growth factor binding proteins, and leptin are present in fetal blood and correlate with birth weight, length, and head circumference (Lo et al 2002). IGF-1 directly influences fetal head and body

growth, and knockout models show its critical role beyond growth hormone alone. IGF-2, expressed in placental endocrine cells, promotes protein synthesis, metabolism, prolactin release, and steroidogenesis—key to increasing fetal mass (Liu, Leroith 1999; Lopez-Tello et al 2023). IGF-1 functions as a nutrient sensor, adjusting growth to glucose and oxygen availability, while IGF-2 enlarges the placenta to enhance nutrient transfer. Their activity is modulated by thyroid hormones and glucocorticoids, adapting to developmental stage and hormone levels to support proliferation, differentiation, and tissue expansion (Fowden, Forhead 2013).

3.5. Leptin and the endocrine-placental crosstalk

While leptin is commonly known as an appetite regulator, this hormone—secreted by both adipose tissue and the placenta—also plays crucial roles in energy balance, reproductive function, and fetoplacental signaling. It regulates gonadotropin production, blastocyst formation and implantation, and modulates trophoblast proliferation, protein synthesis, invasion, and apoptosis. Dysregulated leptin levels are associated with reproductive and gestational disorders, including polycystic ovary syndrome, recurrent miscarriage, gestational diabetes, preeclampsia, and intrauterine growth restriction (Pérez-Pérez et al 2018).

3.6. Thyroid hormones in fetal development

Thyroxine-binding globulin transports ~75 % of circulating thyroxine and a significant portion of triiodothyronine. In peripheral tissues (e.g., liver and kidneys), thyroxine is converted into the active form triiodothyronine by deiodinases (Braithwaite 2015). Early fetal thyroid function depends on maternal iodine and hormone supply until mid-pregnancy (Mégier et al 2023).

Thyroid hormones regulate protein, fat, and carbohydrate metabolism in fetus and neonate, and are essential for brain development, with the fetus relying on maternal thyroid hormones supply until mid-gestation (Raymond, LaFranchi 2010; Moog et al 2017). In sheep fetuses, thyroxine levels correlate positively with oxygen uptake and glucose oxidation, implicating thyroid hormones in near-term fetal oxygen utilization (Fowden, Silver 1995). In human fetuses, low thyroid hormone levels impair hepatic and muscular gene expression, growth, and thermogenesis, and are essential for mediating cortisol's effects on lung maturation and the metabolic transition at birth (Fowden 1995).

Thyroid hormones, particularly triiodothyronine, play essential roles in fetal metabolic regulation, organ maturation, and perinatal adaptation, with early development relying on maternal hormone supply and iodine availability.

3.7. Fetal adrenal axis and cortisol regulation

Adrenocorticotropic hormone is detectable in fetal plasma from around the 12th week, with its levels peaking around the 20th week and remaining high until

approximately 34 weeks, which drives significant adrenal gland growth. During this period, the fetal adrenal glands produce large amounts of dehydroepiandrosterone, while cortisol synthesis gradually increases later in gestation. While cortisol appears in the fetus by the 10th week from maternal and placental sources, endogenous fetal cortisol production progressively contributes to metabolic fetal regulation and tissue maturation (Lofti et al 2018; Mastorakos, Ilias 2003).

Excess maternal cortisol is inactivated to cortisone by placental 11β-hydroxysteroid dehydrogenase type 2, protecting the fetus (Causevic, Mohaupt 2007). Only ~15 % of maternal cortisol remains active in fetal circulation (Murphy et al 1974; Gitau et al 1998). Later in pregnancy, placental 11β-hydroxysteroid dehydrogenase type 2 activity decreases, allowing more active cortisol to reach the fetus, supporting lung and gut maturation (Baibazarova 2013). The levels of cortisol, adrenocorticotropic hormone, and corticotropin-releasing hormone progressively increase until term, reflecting the activation of the maternal and fetal hypothalamic–pituitary–adrenal axis, and gradually decrease after birth, accompanying the normalization of endocrine function (Mastorakos, Ilias 2003; Johnston et al 2018).

The maturation of the fetal adrenal axis, regulated by adrenocorticotropic hormone and modulated by placental cortisol metabolism, is crucial for organ development and metabolic adaptation in late gestation and around birth.

3.8. Antenatal corticosteroids and perinatal outcomes

Antenatal corticosteroid therapy reduces risks of respiratory distress syndrome, intraventricular hemorrhage, and periventricular leukomalacia in preterm infants born up to 34 weeks of gestation. However, it does not impact necrotizing enterocolitis, retinopathy, or bronchopulmonary dysplasia (Roberts, Daiziel 2006). Evidence also suggests caution with corticosteroid use beyond 36 weeks and 6 days, as studies in elective term cesarean deliveries have reported associations with adverse neonatal outcomes (Pei, Chen 2024).

4. Physiological challenges and adaptations during embryonic and fetal development

Embryonic development includes four stages: fertilization and implantation, cell differentiation, organogenesis, and preparation for life outside the womb. The pre-embryonic (weeks 1–2) and embryonic (weeks 3–8) stages establish the body plan and organ foundations, marking the transition to the fetal phase (O'Rahilly, Müller 2010). To meet the increasing energy demands of pregnancy, maternal tissues and the placenta shift toward enhanced oxidative phosphorylation, resulting in the controlled generation of reactive oxygen species that participate in cellular signaling. However, excessive oxidative phosphorylation and reactive oxygen species overproduction can disrupt redox balance and contribute to gestational complication (Sanchez-Aranguren, Nadeem 2021). Each stage depends on nutrient and oxygen

availability, shaped by maternal health and nutritional status. Early-life adaptations influence long-term metabolic, immune, and organ function, with lasting effects on health and disease risk (Simon, Keith 2008; Jain 2020; Reynolds et al 2022).

The progression of embryonic and fetal development depends on tightly regulated metabolic and signaling environments, with early-life conditions shaping organ formation, postnatal adaptation, and long-term health outcomes.

4.1. Oxygen tension shaping the embryonary nest

Early embryonic development occurs under hypoxic conditions, as shown by in situ partial oxygen pressure measurements indicating placental oxygen tension around 18 mmHg (2.5 %) during weeks 8–10 (Rodesch et al 1992). Oocytes rely on cumulus cells for pyruvate, supporting adenosine triphosphate production via oxidative phosphorylation, as oocyte glycolysis is inactive and Complex I activity is low (Sigiura et al 2008; Collado-Fernandez et al 2012; Richani et al 2021). Under reduced oxygen (20–34 mmHg in Fallopian tubes), lactate production via anaerobic glycolysis predominates (Gull et al 1999; Redel et al 2012; Rodriguez-Nuevo et al 2022). Despite low oxygen availability, oocyte and embryo respiration remains stable, with progressive increases in mitochondrial activity through the blastocyst stage (Mills, Brinster 1967). The trophectoderm demonstrates higher metabolic demand compared to the inner cell mass. From approximately week 12, spiral artery remodeling enhances maternal blood flow and raises placental oxygenation (Wang et al 1995; Burton, Jauniaux 2010; Schneider 2011), reaching 45–50 mmHg by weeks 14–16. This transition is regulated by hypoxia-inducible factors (HIF), particularly HIF-1, which coordinate angiogenesis, cellular differentiation, and placental maturation in response to oxygen levels (Wang et al 1995). Beyond placental changes, fetuses exhibit adaptive mechanisms to transient or chronic hypoxemia, including blood flow redistribution and modulation of heart rate, ensuring oxygen delivery to vital organs and preservation of metabolic stability (Martin 2008). As oxygen availability gradually increases, aerobic metabolism is favored in parallel with accelerated fetal growth and reduced cellular proliferation (Genbacev et al 1996,Fathollahipour et al 2019).

The shift from a low-oxygen intrauterine environment to increased placental oxygenation marks a pivotal metabolic transition that supports differentiation, energy demands, and placental maturation across developmental stages.

4.2. Energy metabolism in early embryogenesis

During early embryogenesis, hypoxia is present; however, mitochondrial respiration persists through alternative dehydrogenases that bypass Complex I, sustaining the tricarboxylic acid cycle and the synthesis of essential metabolites such as heme. In agreement with the 'quiet embryo hypothesis,' moderate and regulated metabolic activity is a hallmark of developmental competence, with mitochondria favoring efficient ATP production while limiting reactive oxygen species generation during the zygote-to-morula stages (Cummins 2001; Houghton 2021; Leese 2002;

Zhao et al 2023;). Concurrently, a Warburg-like metabolic profile has been observed in rapidly proliferating embryos, indicating stage-specific metabolic strategies (Krisher, Prather 2012). These adaptive mechanisms highlight how oxygen availability modulates reactive oxygen species levels and preserves cellular homeostasis under low-oxygen conditions (Sen et al 2024).

Hormonal changes modulate tubal metabolite levels to support fertilization and early embryonic development. Glucose drops from 3 mM (follicular) to 0.5 mM (midcycle), rising to 2 mM (luteal). Lactate increases from 5 to 10 mM at ovulation; pyruvate remains stable at 0.1 mM. In contrast, uterine fluid remains constant (glucose 3 mM, lactate 6 mM, pyruvate 0.1 mM) (Gardner et al 1966). These metabolic shifts reflect the tubal environment's dynamic role, with even greater variation expected during implantation and the cumulus cell supporting early embryonic development.

Oxygen consumption of fertilized rabbit ova at different developmental stages was measured with various metabolites and inhibitors. Pre-incubation for up to 3 hours did not reduce endogenous respiration, and added glucose or pyruvate had no impact, suggesting the presence of non-glucose intracellular energy stores. Glycolytic activity appeared only in late morulae and blastocysts with exogenous glucose, reflecting the developmental emergence of specific enzyme systems (Fridhandler et al 1957). Pyruvate was the primary energy source until the blastocyst stage on day 5, after which glucose metabolism and oxygen uptake increased, signaling a shift to oxidative metabolism with additional contributions from amino acids, lactate, and fatty acids (Fridhandler et al 1957; Leese 2012). Mitochondrial integrity remains central to these transitions, as highlighted by studies on oocyte competence and embryo viability (Babayev 2015; Qi et al 2019). Mitochondrial activity underpins these transitions and supports developmental competence. In porcine blastocysts, physiological hypoxia shifts metabolism from oxidative phosphorylation to glycolysis, with reduced oxygen tension (5–10 %) improving inner cell mass-to-trophectoderm ratio and developmental potential during *in vitro* culture (Karja 2004).

Early embryonic development relies on tightly regulated metabolic adaptations to hypoxia, favoring efficient ATP production with minimal oxidative stress, while dynamic shifts in substrate availability and oxygen levels guide the transition toward oxidative metabolism and blastocyst formation.

4.3. Aerobic glycolysis and lactate as a metabolic signal

The Crabtree, Pasteur and Warburg effects are key examples of cellular adaptations to varying oxygen and glucose availability. In the Warburg effect, tumor cells preferentially undergo aerobic glycolysis, converting glucose to lactate even in the presence of oxygen, a process that supports rapid ATP generation and biosynthesis while oxidative phosphorylation remains functional (Chen et al 2015).

The Crabtree effect occurs when high glucose concentrations suppress mitochondrial respiration, promoting fermentation even under aerobic conditions

(Kumar et al 2017). In contrast, the Pasteur effect is classically defined as an increase in glycolysis under low oxygen conditions to compensate for reduced ATP yield (Barker et al 1964), though similar metabolic switching has also been observed in germ cell reprogramming models (Moratilla et al 2021). Developing embryos exhibit metabolic traits reminiscent of tumor cells, such as persistent aerobic glycolysis even under oxygen-rich conditions (Zhao et al 2023; Redel et al 2012; Smith, Sturmey 2013; Shahzad et al 2020; Wang et al 2023; Li, Ye 2024). At the two-cell stage, glucose availability enhances lipid biosynthesis, highlighting the stage-specific metabolic plasticity required for early embryonic development (Wang et al 2023).

In murine embryos, the transition from the morula to the blastocyst stage is characterized by an upregulation of glycolysis and specific amino acid pathways, accompanied by a relative decrease in tricarboxylic acid (TCA) cycle activity, with lactate emerging as the predominant metabolic end product (Lane and Gardner, 1996; Gardner, 1998). This reprogramming supports the proliferative demands of early embryonic development and mirrors the Warburg-like phenotype also observed in porcine embryos (Redel et al, 2012), At the implantation site, lactate contributes to microenvironmental acidification, facilitates trophoblast invasion, and promotes angiogenesis through VEGF signaling pathways (Ruan, Kazlauskas 2013). Additionally, lactate modulates maternal immune responses, supporting immune tolerance at the maternal–fetal interface. Acting both extracellularly and intracellularly, lactate influences gene and protein expression in blastocyst and endometrial (Tian and Zhou, 2022; Gurner and Gardner, 2025) cells via mechanisms such as protein lactylation (Zhao et al, 2024). In the past lactate was considered a waste, but now it is viewed as : (1) a significant energy source, (2) the major gluconeogenic precursor, and (3) a signaling molecule. ‘‘Lactate shuttle’’ is a key to better comprehension of cell reproduction in cancer, embryogenesis, fixation on tissues, and control of immune implantation of cells (Brooks, 2018; Wang et al, 2024).

4.4. Implantation and the hypoxia-inducible factor

During implantation, the oxygen tension in the maternal plasma surrounding the placental villi remains below 20 mmHg until approximately 10–12 weeks of gestation, after which it increases to 40–80 mmHg and stays within this range throughout the second and third trimester (Tuuli et al 2011) which is essential for maintaining the high proliferation and limited invasiveness of the immature trophoblasts.

HIF is a heterodimeric transcription factor that mediates cellular adaptation to low oxygen availability. Under normoxic conditions, HIF undergoes hydroxylation and subsequent ubiquitin-mediated degradation; however, under hypoxia, this process is inhibited, allowing HIF to accumulate and activate target genes involved in angiogenesis, glycolysis, and erythropoiesis. (Wang et al 1995; Déry et al 2005; Ziello et al 2007; Benita et al 2009; Fajersztajn, Veras 2017; Nagao et al 2019; Colson et al 2021). Regulation of HIF stability extends beyond oxygen availability, as multiple factors modulate HIF levels, including cellular oxidants. Notably, mitochondrial reactive

oxygen species can stabilize HIF under normoxic conditions, thereby enhancing the expression of vascular endothelial growth factor and glycolytic enzymes (Chandel et al 2000). Additionally, the accumulation of tricarboxylic acid cycle intermediates such as succinate and fumarate inhibits prolyl hydroxylases, further preventing HIF degradation and sustaining its transcriptional activity (Martinez-Reyes, Chandel 2020). Together, these mitochondrial mechanisms can integrate HIF-dependent adaptation to metabolic and environmental cues.

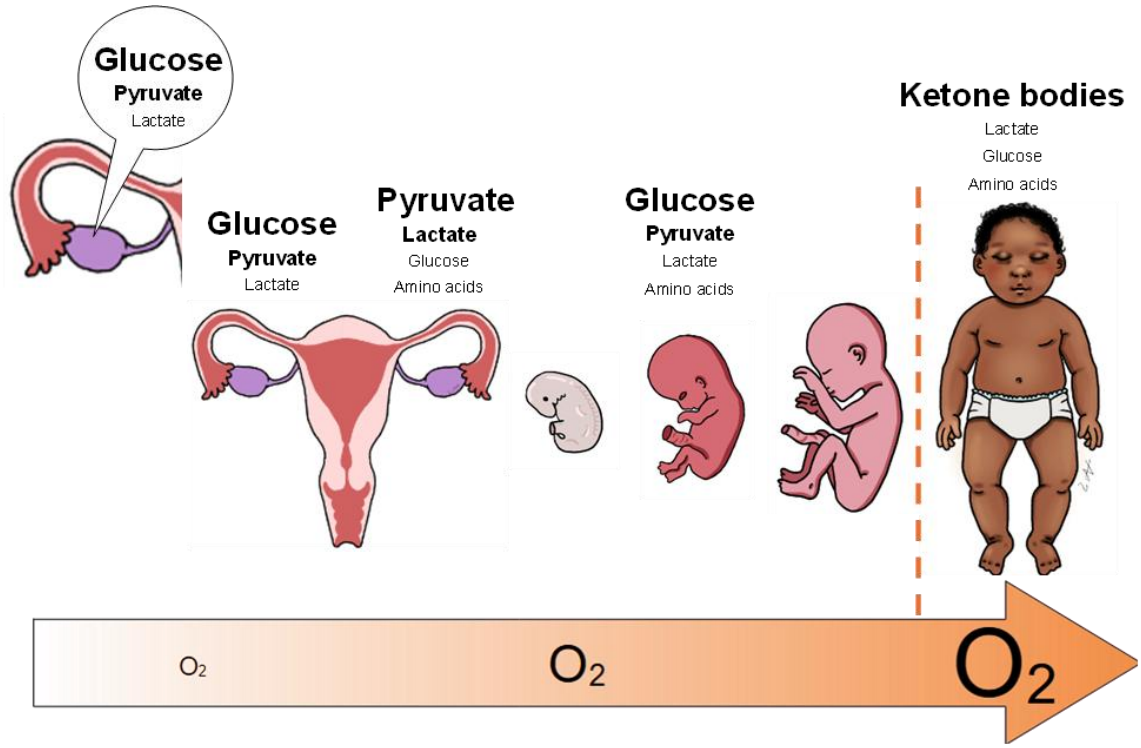

Figure 1. Oxygen metabolism and nutrient preferences along human embryonic development. Zygote implantation occurs under chronic low oxygen tensions, steadily shifting towards mild hypoxia close to normoxia until the labor process begins. During this time, the fetus faces acute and severe hypoxic stress, which is alleviated only after the newborn emerges into an extra-uterine environment. Several physiological adaptations to overcome hypoxia are engaged during human development, and nutrient preferences are determined to meet specific embryonic and fetal energy demands. Illustration by Luana M. Fernandes.

HIF-1α and HIF-2α enhance glycolysis under hypoxia (Seagroves et al 2001), and in primordial germ cells they drive cellular reprogramming through PKCε inhibition (Redel et al 2012).

Transforming growth factor beta-3 expression in trophoblasts during hypoxia is mediated by HIF-1α, supporting implantation, nutrient exchange, and placental blood flow (Caniggia et al 2000). As oxygen levels increase, the decline in HIF-1α coincides with the upregulation of α-integrin expression, which enhances trophoblast invasiveness (Dzierzak, Philipsen 2013). During hypoxia, upregulation of transaldolase

1 and pyruvate dehydrogenase kinase 1 redirects metabolites from the pentose phosphate pathway to glycolysis while inhibiting the tricarboxylic acid cycle, allowing preimplantation embryos to meet energy demands through enhanced glycolytic activity. This metabolic shift, consistent with the Warburg effect, supports rapid proliferation (Krisher, Prather 2012; Redel et al 2012).

The roles of hypoxia and HIF-mediated signaling are essential in regulating trophoblast behavior, metabolic reprogramming, and vascular development, all of which help create a supportive environment for successful implantation and early placental function.

4.5. Fetal hemoglobin

Primitive nucleated erythrocytes arise in yolk-sac blood islands shortly after implantation, expressing embryonic globin (Dzierzak, Philipsen 2013). Yolk-sac hematopoietic progenitors generate primitive erythrocytes as well as early myeloid and definitive erythroid precursors; with further development, circulating stem/progenitor cells seed the fetal liver, and later the spleen and bone marrow, where they establish myeloid and lymphoid lineages within supportive niches (Moore et al 1967; Dzierzak, Philipsen 2013). Fetal hemoglobin synthesis begins around six weeks of gestation, becomes the predominant hemoglobin form by 10–12 weeks, and remains the major oxygen carrier until approximately six months after birth (Dame, Juul 2000).

Fetal hemoglobin exhibits intrinsically higher oxygen affinity than adult hemoglobin, a property regulated allosterically and further modulated by electrostatic interactions with chloride ions and organophosphate anions. This enhanced affinity is largely explained by the reduced binding of γ-globin to 2,3-bisphosphoglycerate compared with β-globin in HbA, thereby facilitating efficient maternal–fetal oxygen transfer (Poyart et al 1992; Pritišanac et al 2021).

The leftward shift of the fetal oxygen dissociation curve enhances O_2 uptake from maternal blood. Hemoglobin cooperativity optimizes loading, while elevated CO_2 and acidity in fetal tissues trigger the Bohr effect, reducing affinity and promoting O_2 release. In combination with the intrinsic differences in oxygen affinity between fetal and adult hemoglobin, and the interplay of maternal–fetal Bohr and Haldane effects, this system maximizes placental oxygen transfer (Zhang et al 2003; Zhang et al 2006; Pritišanac et al 2021).

The development of fetal hematopoiesis and the unique properties of fetal hemoglobin ensure efficient oxygen transport and delivery under low-oxygen conditions, supporting the growing metabolic needs of embryonic and fetal tissues throughout gestation.

4.5.1. Fetal blood partial pressures of gases and temperature

Fetal hemoglobin oxygen release is modulated by pH, oxygen and carbon dioxide pressures, and temperature (Poyart et al 1992; Woyke et al 2022). In early pregnancy,

placental oxygen tension remains low until about 11 weeks, then rises to establish a maternal–fetal gradient by the fourth month. This transient hypoxia supports trophoblast proliferation and may protect the embryo from oxygen-induced toxicity (Burton et al 2021).

As fetal energy demands rise, aerobic metabolism increases oxygen use. Hemoglobin releases oxygen and binds more carbon dioxide (Haldane effect), enhancing its transport to the placenta (Lang, Brubakk 2009). In the maternal lungs, the exhalation of carbon dioxide increases blood pH and raises the oxygen affinity of hemoglobin A. The Bohr effect further adjusts hemoglobin's oxygen affinity according to the maternal acid–base status (Malte et al 2021), while temperature influences hemoglobin dissociation (Christmas, Bassingthwaighte 2017; Woyke et al 2022). There, oxygen is taken up and carbon dioxide released, ensuring effective fetal gas exchange and maintaining metabolic acid-base balance. In maternal lungs, carbon dioxide exhalation raises pH and boosts hemoglobin A's oxygen affinity, enhancing uptake and transfer to the fetus (Lang, Brubakk 2009; Nye et al 2018; Malte et al 2021). Fetal blood is ~0.4 °C warmer than maternal blood, with heat transferred via the umbilical cord, while brain thermoregulation ensures stability (Jauniaux et al 2001). Experimental data in mammalian models indicate that temperature can modulate hemoglobin–gas interactions, even when the effect is modest, supporting the concept that slightly higher fetal temperature may influence oxygen release dynamics (Willford, Hill 1986). Mild fetal hyperthermia lowers hemoglobin oxygen affinity, aiding tissue delivery, but fetal hemoglobin retains high affinity even at elevated temperatures, ensuring effective oxygen extraction (Poyart et al 1992; Asakura 2004; Christmas, Bassingthwaighte 2017).

The interplay of fetal hemoglobin molecular adaptations (Poyart et al 1992), thermoregulatory adjustments including right-shifted dissociation curve and maternal–fetal heat transfer (Asakura 2004), and temperature-dependent solubility changes in respiratory gases (Christmas, Bassingthwaighte 2017) ensures efficient oxygen delivery and carbon dioxide removal, supporting the elevated metabolic demands of the growing fetus while maintaining homeostasis throughout pregnancy.

4.5.2. Fetal blood flow

Fetal blood flow is essential for delivering oxygen and nutrients to support proper development during pregnancy. This process relies on maternal circulatory adaptations, strongly influenced by sex steroid hormones such as estradiol, which reduce uterine vascular resistance and enhance blood flow (Maliqueo et al 2016). During pregnancy, maternal stroke volume rises by about 30 % due to reduced vascular resistance, contributing to lower blood pressure, improved placental perfusion, and enhanced cardiac stability (Costantine 2014). Maternal cardiac output increases through higher heart rate and stroke volume, ensuring effective nutrient and oxygen delivery. Coordinated adjustments in uteroplacental and umbilical-placental

circulation are crucial to sustain a steady nutritional supply as pregnancy progresses (Osol et al 2019; Ling et al 2021).

Oxygen-rich blood from the placenta is delivered to the fetus through the umbilical vein, while blood carrying carbon dioxide is returned to the placenta via the umbilical arteries. Adaptive changes in fetal circulatory pressure and heart rate enhance oxygen delivery to fetal tissues supporting their growth.

5. Metabolic constraints and adaptations during fetal development and delivery

Fetuses are classified by size relative to gestational age: appropriate, small, or large. Appropriate-size fetuses show higher levels of branched-chain amino acids, supporting energy production and growth, while small ones have reduced essential amino acids. Maternal amino acid levels, including glycine and lysine, correlate with fetal growth. Low early protein intake may initially impair growth but later increase body weight, while blastocyst abnormalities resulting from maternal undernutrition are linked to elevated blood pressure in later life (Moghissi et al 1975; Cetin et al 1990; Kwong et al 2000).

Preventing small-for-gestational-age outcomes is the most promising strategy for reducing the intergenerational risk of type 2 diabetes (Hernández, Mericq 2000), and these prevention are the most promising strategy for reducing the intergenerational risk of metabolic disease (Barker 1995). Epidemiological studies, including those from the 1945 Dutch famine, demonstrate that malnutrition at any stage of pregnancy causes glucose intolerance and increases long-term risks of metabolic disease (Roseboom et al 2006).

Fetal energy metabolism evolves throughout development, with glucose as the primary fuel. The fetal liver increases glucose uptake during pregnancy, influenced by maternal insulin resistance (Hay 2006). Gluconeogenesis remains minimal until birth due to low expression of phosphoenolpyruvate carboxykinase. After delivery, phosphoenolpyruvate carboxykinase activity rises sharply, triggered by a surge in cortisol and catecholamines, coupled with a decrease in the insulin-to-glucagon ratio, which collectively coordinate the neonatal metabolic transition (Girard 1986; 1990). In well-nourished pregnancies, gluconeogenesis is unnecessary. Under poor maternal nutrition, fetal metabolism adapts by upregulating gluconeogenesis to preserve glucose supply. This shift may impair placental nutrient transport and insulin sensitivity, increasing the risk of growth restriction and future metabolic disorders (Goodner, Thompson 1967; McCurdy, Friedman 2006; Şengül, Dede 2014).

Glucose is the primary energy source for fetal growth, and its fluctuating availability prompts metabolic adaptations across developmental stages. In sheep, fetal glucose utilization increases with higher glucose and insulin, indicating insulin-dependent control of carbohydrate metabolism (Hay et al 1988). In humans, altered glucose homeostasis due to maternal diabetes, malnutrition, drug exposures, genetic

conditions, or obesity can impair development (Agarwal et al 2018; Ashon et al 2018; Parrettini et al 2020; Saini et al 2023).

Hyperglycemia can suppress oxidative phosphorylation and compromise ATP production during early development, as observed in gestational diabetes. It also induces phenotypic alterations in lipid metabolism, leading to intracellular lipid accumulation (steatosis) within cytotrophoblasts of placentas from pregnancies affected by gestational diabetes (Valent et al 2021).

During early development, endogenous lipid metabolism provides energy, supports membrane biogenesis and regulates signaling; stage-specific lipidome remodeling includes increasing phospholipid unsaturation toward the blastocyst and dependence on desaturases such as SCD1 (Zhang et al 2024). Lipids provide energy, support membrane synthesis, and regulate signaling (178). In porcine oocytes, palmitic, oleic, and linoleic acids predominate, suggesting roles in oocyte maturation and embryonic progression (McEvoy et al 2000).

This pattern appears to be driven by increased linoleic acid uptake, essential for maintaining membrane fluidity and supporting metabolic demands during early cell divisions. Human preimplantation embryos are enriched in unsaturated fatty acids, especially linoleic acid, which supports membrane flexibility during rapid cell divisions (Haggarty et al 2006). The importance of fatty acid transport in embryogenesis is highlighted by studies in mice showing that fatty acid transport protein 4 (FATP4) is essential for embryonic viability and long-chain fatty acid uptake in extraembryonic tissues, suggesting a conserved role in early development (Gimeno et al 2003).

After placentation, essential fatty acids such as docosahexaenoic and arachidonic acids, derived from the maternal diet, are transferred through the placenta and support fetal development (Duttaroy 2009). Evidence from animal studies indicates that maternal high-fat diets can transiently reduce offspring weight, while metabolic reviews emphasize that lipids alone cannot meet fetal energy needs without adequate carbohydrate supply (Hausman et al 1991; Zeng et al 2017). Overall, fetal glucose and lipid metabolism, tightly regulated by maternal nutrition, hormones, and placental transport, ensure energy availability, cell growth, and readiness for birth.

Maternal metabolism transitions from an anabolic state in early pregnancy to a catabolic state in late gestation, with hormonally driven insulin resistance, fat mobilization and greater fatty-acid oxidation. These adaptations prioritize a continuous fetal glucose supply while increasingly meeting maternal energy demands via lipid metabolism (Lindsay et al 2015; Zeng et al 2017). Ketone bodies readily cross the placenta and may serve as alternative energy substrates for fetal tissues; however, their functional relevance and safety, particularly for the developing fetal central nervous system, warrant cautious interpretation in the context of complicated pregnancies (Bronisz et al 2018).

In laboratory models, rabbit embryos are able to undergo cleavage during the first 48 hours without an exogenous nitrogen source, although the presence of amino acids

and carbohydrates enhances their developmental performance (Kane 1987). Certain amino acids in culture enhance blastocyst formation and viability: proline may activate pro-growth pathways (e.g., mTOR-related), glutamine supports blastocyst development and improves bioenergetics, glycine functions as an osmoprotectant, and methionine is critical during cleavage stages (Chen et al 2018; Morris et Van Winkle 2021). At the blastocyst stage, leucine and arginine promote trophoblast motility through mTOR-dependent signaling, thereby supporting implantation competence; meanwhile, maintenance of pluripotency in inner cell mass cells involves specific amino acid requirements (González et al 2012).

While early mammalian embryos can undergo initial development relying on intrinsic energy stores, the inclusion of specific amino acids in culture media fundamentally enhances embryo viability and blastocyst formation by supporting key metabolic, structural, and regulatory processes essential for growth, differentiation, and successful implantation.

6. Physiological and metabolic adaptations in neonatal life

Human birth typically occurs around 40 weeks of gestation, marking the fetus's transition to extrauterine life. While fetal glucocorticoids are essential for preparing the fetus for this transition, their role in initiating labor in humans—unlike in other mammals—remains unclear. Consequently, predicting the onset of spontaneous labor continues to be a significant clinical challenge. Despite advances in maternal biomarkers, this imprecision increases the risk of adverse outcomes and complicates obstetric management (Stelzer et al 2021).

After birth, arterial oxygen saturation rises sharply as spontaneous ventilation and pulmonary blood flow are established. This transition enhances carotid body chemoreceptor sensitivity and coincides with the rapid postnatal decline of HIF-1α protein levels, reflecting the developmental resetting of oxygen sensing and metabolic adaptation to extrauterine life (Girard 1990; Roux et al 2005; Resnik et al 2007).

Immediate cord clamping abruptly interrupts maternal glucose and insulin supply, leading to reduced neonatal plasma glucose and insulin and concomitant increases in glucagon, catecholamines, and cortisol. The resulting shift in the insulin/glucagon ratio rapidly induces hepatic gluconeogenesis through upregulation of phosphoenolpyruvate carboxykinase and enhanced fatty acid oxidation, as described in mechanistic studies (Girad, 1986; Platt, Deshpande 2005). Transient neonatal hypoglycemia further contributes to this metabolic transition, ensuring adequate energy delivery during adaptation to extrauterine life, with clinical implications highlighted in recent reviews (Harding et al 2024).

Full-term newborns display higher energy expenditure per minute than fetuses, reflecting the abrupt shift from a thermally regulated intrauterine environment to variable, energy-demanding external conditions. This increase is supported by studies quantifying neonatal versus fetal energy needs (Brooke 1985) and by mechanistic

evidence of metabolic pathway activation at birth, such as the rapid emergence of gluconeogenesis and fatty acid oxidation (Harding et al 2024). Neonates require increased metabolic output for thermal regulation, spontaneous muscular activity, and accelerated growth. Vaginal birth amplifies the neonatal stress response and energy mobilization—marked by surges in stress hormones and heightened activation of brown adipose tissue for non-shivering thermogenesis—thus potentially promoting earlier metabolic adaptation versus cesarean delivery, which blunts these adaptive thermal responses (Lubkowska et al 2020; Asakura 2004; Aherne, Hull 1996).

Cesarean-born infants generally require a longer period to achieve optimal oxygen saturation during the first minutes after birth, reflecting delayed physiological adaptation compared with vaginal delivery (Lubkowska 2020; Lara-Cantón et al 2024). Regardless of delivery mode, neonates experience transient reductions in oxygenation during the immediate postnatal transition, accompanied by coordinated metabolic adjustments—such as activation of gluconeogenesis and fatty acid oxidation—that ensure adequate energy availability (Girard 1990; Platt, Deshpande 2005).

The transition from fetal to neonatal life involves coordinated physiological adjustments, including pulmonary fluid clearance, initiation of spontaneous respiration, circulatory remodeling, activation of metabolic pathways, and thermoregulatory control. These processes are largely driven by prepartum surges in cortisol and catecholamines occurring around the time of labor and delivery (Cawson et al 1974; Girard 1990; Lara-Cantón et al 2024).

Evidence indicates that infants delivered via spontaneous vaginal birth exhibit the highest cord blood cortisol concentrations compared with those born through assisted or cesarean delivery, reflecting a more pronounced activation of the fetal hypothalamic–pituitary–adrenal axis during labor. Such hormonal surges are critical for both the onset of labor and the immediate postnatal physiological adaptation (Mastorakos, Ilias I 2003; Stjernholm et al 2016).

Neonatal energy expenditure correlates closely with heart rate, which averages about 140 beats per minute in early infancy and gradually declines as children grow, reaching lower values toward late adolescence (Finley, Nugent 1995; Treuth et al 1998).

This trajectory reflects allometric scaling: metabolic rate and physiological stress decrease relative to body mass as individuals mature, signifying lower metabolic demands per unit of tissue from infancy through adulthood (West et al 2002). White blood cells are highest at birth, reflecting the physiological stress of delivery and increased metabolic activity. These values decrease progressively during infancy and continue to decline throughout life, in parallel with the gradual reduction in growth rate, tissue renewal, and metabolic demands (Manroe et al 1979; McGrath et al 1982).

Immediately after birth, the newborn's energy supply shifts to internal reserves, primarily stored fat, making human newborns the most fat-rich among mammals (Kuzawa 1998). In the first hours of life, they rely on hepatic glycogen, which

accumulates late in gestation and serves as a crucial energy source during the metabolic transition at birth. However, with the cessation of transplacental glucose transport, glycogen stores are rapidly depleted, necessitating the activation of gluconeogenesis (Kalhan, Parini 2000). Gluconeogenesis is not as significantly limited by the metabolic demands of parturition; instead, it still plays a vital role in maintaining blood glucose levels after parturition. (Kalhan, Parini 2000). Lactate also serves as an important alternative energy substrate after birth to brain, in murine the generating of ketone bodies in the liver to support, heart, liver, brain and lipogenesis during the immediate postnatal period, suggesting that can occurs in human newborn (Medina 1985; Almeida et al 1992).

Cardiovascular circulation shifts at birth as pulmonary aeration redirects blood flow to the lungs and venous return to the left atrium (Tan, Lewandowski 2020). In cold environments, newborns conserve heat via peripheral vasoconstriction and non-shivering thermogenesis in brown adipose tissue (Aherne, Hull 1966; Hey et al 1970; Wu et al 1980). In the first week, term appropriate-for-gestational-age infants are capable of ketone production, whereas preterm and SGA infants have lower ketogenesis and higher hypoglycemia risk (Hawdon et al 1992). Newborns adapt metabolically by shifting insulin and glucagon levels, activating glycogenolysis, and increasing lipolysis to maintain energy. The brain, consuming more than half of total energy, relies on these processes (Georgieff et al 2018). Fetal growth correlates with brain size, favoring larger infants (Nivins et al 2023). Initially, colostrum provides immune protection and supports gut development, though it offers little energy (Ballard, Moeeow 2013) and during this phase, newborns may lose up to 10 % of birth weight (Macdonald et al 2003). Postpartum changes in milk composition should be regarded as part of a continuum, characterized by rapid alterations during the first four days after delivery, followed by more gradual modifications in various milk components throughout the remainder of lactation (Neville et al 2001). At birth, newborns must adapt to a sudden increase in reactive oxygen species due to heightened oxygen exposure (Friel et al 2004).

This transition is managed through multiple antioxidant mechanisms, including enzymatic defenses, cofactors, and scavenger molecules. A key adaptation is the breakdown of fetal red blood cells, which can lead to neonatal jaundice. Bilirubin, a byproduct of hemoglobin degradation, plays a dual role: while excessive levels can be neurotoxic at physiological concentrations, it acts as an antioxidant, helping to counteract oxidative stress from increased oxygen exposure. Premature infants are particularly vulnerable to both hyperbilirubinemia and oxidative stress, making them more susceptible to reactive oxygen species related damage (Saugstad 1990; Dani et al 2019). In healthy full-term infants, erythropoietin levels are lowest during the first month and peak in the second, inversely correlating with hemoglobin. After birth, high oxygen availability suppresses erythropoietin, reducing reticulocytes and leading to physiological anemia marked by low hemoglobin and red cell counts. Erythropoietin production resumes when hemoglobin falls to about 9.0 g/dL (Kling et al 1996). This

oxygen-rich environment also drives a postnatal shift in hemoglobin composition. Fetal hemoglobin, dominant at birth, gradually declines, reaching approximately 7 % by 52 weeks, while adult hemoglobin becomes the prevailing form, supporting lifelong oxygen transport needs (Bell 1999).

7. Future directions

While the perinatal period is recognized as a critical window for shaping lifelong health, our understanding of many metabolic and environmental interventions remains limited. This recognition is central to the DOHaD framework (Malhotra et al 2014; McKerracher et al 2019). Evidence further highlights that interventions spanning from the preconception period through the first two years of life represent a unique opportunity to support optimal growth and neurodevelopment (Schwarzenberg et al 2018; Stephenson et al 2018). Future research must capture the complexity of this period. Key aspects include:

1. Metabolism and epigenetics: Integrating metabolomics and epigenetics to understand how nutrient availability shapes gene expression via mechanisms like DNA methylation (Wu et al 2023). This includes real-time monitoring of maternal-fetal metabolic profiles to detect stress and guide personalizes nutrition (Monni et al 2021; Yamauchi et al 2021).
2. Fertilization and systems biology: Non-invasive biomarkers and computational modeling of multi-omics data are increasingly applied to dissect regulatory networks and support targeted interventions in fertility and embryology. While promising insights have been obtained in porcine models, careful translational validation is required before extending these findings to human reproduction (Rosenwaks 2017; Puniya et al 2024).
3. Maternal–fetal vaccines: Novel vaccine strategies, including mRNA and protein subunit platforms, are being developed to protect both mother and fetus against infectious diseases and adverse pregnancy outcomes. Some preclinical advances—such as experimental Ebola virus vaccines—have so far been demonstrated mainly in murine models, underscoring the need for translational studies before application in humans (Atyer er al 2022; Prasad et al 2022; Willians et al 2022; Son et al 2024; Medoro, Puopolo 2025).
4. Microbiome therapies: Modulating the maternal and neonatal gut microbiota with prebiotics, probiotics, and other therapies to reduce the risk of allergic and inflammatory diseases in offspring and support balanced immune maturation (Milani et al 2017; Robertson et al 2019; Vandenplas et al 2020).
5. Epigenetic therapies: Exploring agents that modulate epigenetic marks to counteract adverse in utero exposures and reduce long-term disease risk (Siddeek, Simeoni 2022).

Future progress in maternal and infant health will depend on the integration of precision medicine approaches that leverage individual genetic, environmental, and lifestyle factors to predict risks and tailor interventions for pregnancy complications and

long-term well-being. Advancing this agenda also depends on scalable and cost-effective strategies informed by routine health data, pragmatic trials, and predictive modeling. The overarching goal is to identify and expand interventions with the greatest and most equitable impact, thereby improving outcomes, reducing adverse events, and addressing multifactorial conditions with greater accuracy—ultimately advancing maternal–fetal care and establishing a foundation for lifelong and intergenerational health (Bhutta et al 2013, Bauman, Van de Water 2020; Bertozzi et al 2023; Moog et al 2023; Nores et al 2024)

8. Summary and conclusions

Human development is characterized by a programmed sequence of metabolic shifts. Early embryogenesis proceeds in a low-oxygen environment, where metabolism shifts toward glycolysis (a "Warburg-like" effect) to minimize oxidative stress and fuel biosynthesis. As the placenta matures and oxygen delivery increases, metabolism transitions to oxidative phosphorylation to support rapid fetal growth. At birth, the newborn undergoes another critical metabolic reorganization, temporarily relying on glycolysis to manage the stress of transitioning to pulmonary respiration before adopting fatty acids and ketone bodies as primary energy sources.

These metabolic and physiological processes are highly sensitive to maternal health, nutrition, and environmental factors. Through a mechanism known as fetal programming, these exposures can induce lasting epigenetic modifications that determine an individual's long-term health, body composition, and disease susceptibility. This concept, central to the DOHaD framework, underscores the importance of early-life preventive interventions.

Advances in systems biology, multi-omics analysis, and computational modeling are providing unprecedented insight into these complex interactions, enabling the development of personalized medicine. By leveraging these findings, targeted interventions—including precision nutrition, microbiome therapies, advanced vaccines, and epigenetic modulators—can be created and refined. Ultimately, leveraging this knowledge is key to promoting developmental resilience, optimizing maternal and child outcomes, and significantly improving lifelong health and well-being.

Abbreviations

DOHad	Developmental Origins of Health and Disease	HIF	Hypoxia-inducible factor
		IGF	Insulin-like growth factor

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Disclosure of artificial intelligence large language models use

The authors used the AI language models Gemini Pro 2.5 and Perplexity to improve the English language of the manuscript. When revisions were required, the models were prompted with: “Revise the following section to make it clearer and written in native-level English.” The authors retained full responsibility for the manuscript’s content, and all AI-assisted revisions were critically evaluated to ensure that the original scientific information was preserved accurately and precisely.

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