

Impact of the intrauterine environment on future reproductive and metabolic health

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Key content

- As survival of babies born following high-risk pregnancies continues to increase globally, understanding the long-term impacts of suboptimal intrauterine environments on future health becomes increasingly important.
- The intrauterine environment is a key influence on later metabolic health, particularly the tendency to later-life obesity and dyslipidaemia.
- Recent evidence shows that female reproductive function is also highly sensitive to the influence of the early life environment.
- Various suboptimal intrauterine environments are linked to adverse reproductive and metabolic outcomes, including maternal obesity, low-protein diets and chronic fetal hypoxia.

Learning objectives

- To know that the prevalence of high-risk intrauterine environments is increasing in maternity populations because of, for example, increasing rates of maternal obesity.
- To be aware of the later-life health implications for the fetus when caring for women with high-risk pregnancies.
- To understand that children who are survivors of high-risk pregnancies are at increased risk of adverse metabolic health outcomes and more work is required to determine optimal follow-up.

Keywords: developmental programming / high-risk pregnancy / intrauterine environment / metabolic health / reproductive health

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Introduction

Globally, an increasing number of babies are born following exposure to difficult intrauterine environments. This is – at least, partially – attributable to a higher prevalence of risk factors for suboptimal intrauterine environments in the maternity population worldwide; for example, increasing maternal obesity, a higher prevalence of mothers of advanced maternal age and increased incidence of gestational diabetes mellitus (GDM). In the UK, 50% of women of reproductive age are overweight or obese, and one in five women are obese during pregnancy.¹ Moreover, at least 1 in 20 women in the UK are diagnosed with GDM and approximately 1 in 10 is a smoker during pregnancy, making potentially suboptimal intrauterine environments common in the pregnancy population.

Especially in high-resource obstetric settings such as in the UK, there are encouraging recent increases in neonatal survival following exposure to a suboptimal intrauterine environment. This means it is increasingly important to understand in detail the potential long-term health consequences. The traditional pregnancy endpoint of a live-

born baby must be supplemented by considering the long-term health risks for the surviving infant. Obstetricians should particularly consider how the baby's long-term health outcomes might be optimised; for example, by understanding and anticipating potential risks to later health and by optimising the intrauterine environment to mitigate these as far as possible. At present, in clinical practice, these goals remain largely aspirational; however, important recent advances have been made in understanding how the intrauterine environment shapes long-term health and disease risk. Here, we review the latest evidence, with particular reference to life-long metabolic and reproductive health risks.

Developmental programming of health and disease

Evidence from both human cohorts and animal models indicates that even the earliest phases of **embryonic and fetal development are highly sensitive to tiny environmental perturbations.**² During the early pre-implantation phase, recent evidence from studies of rodent embryos shows that

development outside of the female reproductive tract reduces mitochondrial DNA copy number, one of the earliest-adopted proxies of embryo quality.³ With over 7 million children worldwide having been conceived to date using various assisted reproductive technology (ART) techniques, and up to 6% of European babies conceived using ART,⁴ these are findings of widespread interest and significance. Ethical and practical limitations make such effects difficult to study in human pregnancies, hence most interventional studies in this field are performed in animal models. While animal models have limitations in translatability to human pregnancy, many conclusions are supported by observations in human cohorts.

Later in fetal development, there is compelling evidence from both human studies and animal models that maternal diet and weight gain can influence fetal growth and development, with further impacts on health in childhood and later life. The most familiar example in obstetric practice is GDM. If untreated, excess fetal glucose exposure is linked to excessive growth in utero, followed by adverse long-term childhood metabolic outcomes; for example, increased body mass index (BMI) and impaired glucose tolerance.⁵ Other common human pregnancy complications, such as maternal obesity, are also linked to later adverse metabolic outcomes, including high BMI in offspring.⁶ The precise role of the intrauterine environment in linking maternal obesity or diabetes risk to childhood obesity can be difficult to disentangle, especially as shared genetics may predispose both mother and baby to obesity. Mothers and babies also usually share the same family environment, including, for example, the type and quantity of food served at meals, which may be a major influence on obesity risk. However, compelling evidence for an independent role of the intrauterine environment in determining childhood obesity risk comes from studies of previously obese women who were pregnant before and after bariatric surgery. These studies show that children who were in the womb prior to maternal surgery (hence exposed to maternal obesity during their intrauterine development) were significantly heavier by mid-childhood than their siblings born after weight-loss surgery.⁷ Thus, while shared genetics and later environment are clearly important in determining risk of later health outcomes, the intrauterine environment also has a significant impact. Moreover, there may be important differences between the impact of a suboptimal early-life environment on male and female fetuses.⁸

A commonly observed pattern of perinatal growth that predicts later adverse health outcomes in both human studies and animal models is 'catch-up growth', which describes fetal growth restriction followed by accelerated early postnatal growth. It has been suggested the mechanism for catch-up growth in humans may relate to higher basal levels of growth hormone postnatally in children born small for gestational

age.⁹ Evidence from animal models suggests that fetal growth restriction can lead to reduced satiety and blunted response to leptin, ultimately resulting in appetite dysregulation and obesity.¹⁰ Catch-up growth is often viewed as a 'healthy' phenomenon by parents and health workers. However, some evidence suggests that children exhibiting this growth pattern are at increased risk of various adverse metabolic outcomes, including diabetes and obesity.¹¹ This observation is commonly explained by nutrient or oxygen restriction during intrauterine growth leading to various physiological parameters in the fetus; for example, aspects of glucose metabolism being tailored towards a resource-poor environment. This is a useful adaptation if the postnatal environment is also likely to be resource-poor and may confer a survival advantage to offspring who might otherwise struggle to thrive. However, when there is a mismatch between the resource-poor intrauterine environment and the calorie-replete postnatal environment, the newborn is poorly adapted and may be at risk of later pathological complications of excess energy and calorie intake.¹¹ 'Catch-up growth' is currently the focus of research efforts to examine the potential benefits of early childhood interventions to improve long-term metabolic outcomes in human populations.

Mechanisms of developmental programming

The precise molecular mechanisms by which the intrauterine environment might 'programme' the fetus are still being elucidated. However, many studies, particularly those in animal models (which are more easily studied in terms of molecular mechanisms than human cohorts) provide important clues. Although the precise human pathophysiology is probably both complex and multifactorial, we review contributory mechanisms that are likely to be involved in programming metabolic and reproductive dysfunction (summarised in Figure 1).

Epigenetics

Epigenetics is the process of varying gene expression through changing parameters other than the genetic code itself. Although the complete genetic code for any individual is fixed at the time of conception, expression of individual genes varies enormously throughout life and in different cells or tissues. Epigenetic modifications to DNA allow flexible gene expression and hence alter phenotype. One commonly studied epigenetic modification is methylation of DNA at specific sites in the genome that alter promoter or repressor activity for individual genes. Modification of the histones, which are responsible for packaging the DNA into nucleosomes, can also occur through acetylation and render genes more or less amenable to expression. More recently,

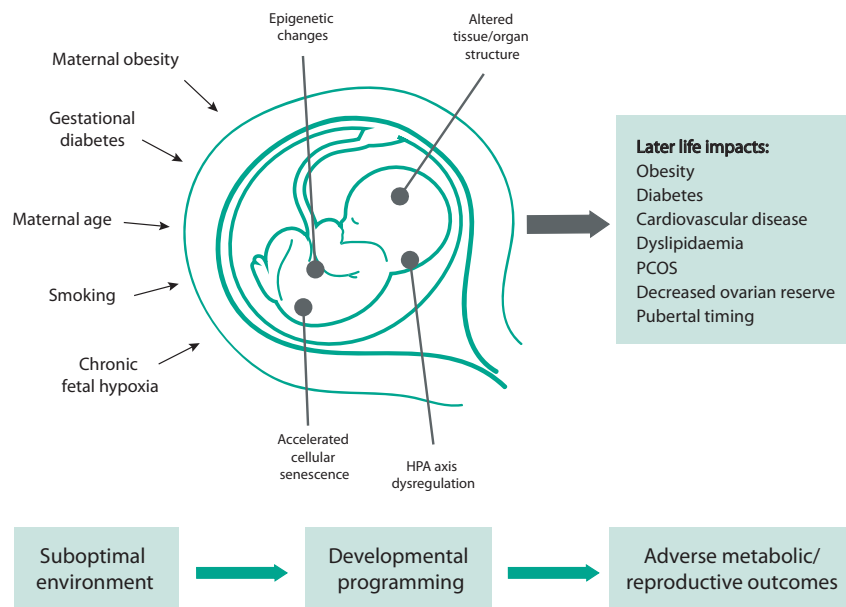


Figure 1. Schematic diagram of putative mechanisms linking the suboptimal early life environment to later adverse metabolic and reproductive outcomes. HPA = hypothalamic–pituitary–adrenal; PCOS = polycystic ovary syndrome.

understanding the vital roles of non-coding RNA (for example microRNAs) has evolved.¹² These small RNAs can bind to various sites on the genome and profoundly alter gene expression. Epigenetic programming can occur periconceptually, antenatally and throughout life with changing lifestyle and environmental factors. However, during fetal life, when cells are rapidly dividing while also changing in morphology and function, epigenetic reprogramming can have a profound effect on the development of anatomical and physiological systems. Examples from human populations include different methylation patterns found in the cord blood of newborns of obese mothers compared with lean mothers.¹³ Altered methylation patterns can persist and continue to influence long-term health in human populations even decades later, as demonstrated in studies of populations exposed to severe maternal malnutrition during intrauterine development.¹⁴

Altered tissue and organ structure

When conditions within the womb are suboptimal, scarce resources are prioritised to ensure fetal survival. Therefore, during organogenesis, the developing fetal brain is protected at the expense of other organ systems; for example, the liver, pancreas, muscle, and adipose tissue. Fetal muscle and adipose tissue are highly sensitive to the metabolic milieu; for example, hypoxia. This is common in severely growth-restricted infants, leading to hypercatecholaminaemia and reduced oxidative glucose metabolism. Fetal glucose utilisation is prioritised in neural tissue at the expense of

muscle, to free resources for neural development. In humans, fetal growth restriction is associated with a reduction in lean mass and ponderal index at birth, which persists into childhood and young adulthood.¹⁵ Studies in animal models show that an altered ratio of lean-to-adipose tissue in offspring not only has immediate effects on neonatal metabolism, but the distribution of fat and muscle also remains altered throughout life.¹⁶

Cellular ageing

Metabolic and reproductive function decline naturally in all organisms as ageing occurs. If this process is accelerated, then early onset pathology results, such as type II diabetes or premature decline in fertility. Adverse conditions in utero could predispose towards early ageing of cells and tissues by disrupting the normal protections against premature ageing.¹⁷ Telomeres, the repeating non-coding DNA sequences that cap the end of each chromosome, are important in protecting chromosomes from DNA damage. As cells face accumulating stresses during life, the telomeres gradually shorten. With each cell division around 30–150 base pairs are lost from each telomere, although DNA repair mechanisms and the activity of telomerase can help to compensate for some of this loss. When telomeres reach critically short lengths, this triggers cellular senescence. Cells and tissues that accumulate excess damage early in life, for example, through exposure to a suboptimal intrauterine environment, age faster, thus display more pathological phenotypes (such as diabetes and obesity) earlier in adult life.

Examples from human cohorts include accelerated telomere shortening in children delivered prematurely⁸ and in the placenta following prenatal exposure to GDM.¹⁹

Programming of the hypothalamic–pituitary–adrenal axis

Modulation of the hypothalamic–pituitary–adrenal (HPA) axis, which is integrative in metabolic and reproductive health, may also occur in response to adverse conditions in utero. The primary evidence for programming of the HPA axis comes from animal experiments using synthetic glucocorticoid administration, which results in altered gene expression in the HPA axis. In humans, maternal obesity is associated with alterations in salivary cortisol in a cohort followed through to adulthood,²⁰ suggesting that HPA axis activity may be programmed in utero.

Placenta

The placenta is key in determining fetal outcome, both in the short and long term. **Maternal environmental factors can influence placental phenotype, including size and vascularity.**²¹ In animal models, exposure to high-fat maternal diet or chronic hypoxia results in alteration of placental morphology, particularly the junctional zone. Both animal models and human studies also suggest that **placental nutrient transfer and gas exchange may be influenced by the early life environment, in particular maternal obesity.**^{21,22}

Evidence for developmental programming of specific metabolic effects

Future obesity

The link between human birthweight and future obesity is well established, with a recent study indicating that for every kilogram increase in birthweight there is a corresponding 50% increase in the risk of being overweight by mid-childhood.²³ Maternal obesity is linked to both fetal macrosomia and growth restriction; these are both independent risk factors for future obesity and for other aspects of the metabolic syndrome phenotype.²⁴ The independent effects of maternal obesity and maternal hyperglycaemia on the risk of childhood adiposity are complex to disentangle, as these often coexist in human cohorts. For example, follow-up of the HAPO (Hyperglycaemia and Adverse Pregnancy Outcomes) cohort²⁵ shows increased risk of adiposity by mid-childhood in the offspring of mothers with GDM; however the impact was less when corrected for maternal BMI. Several recent studies give new mechanistic insights into the association between maternal BMI and later adiposity in offspring.² Mesenchymal stem cells derived from umbilical cord blood of humans show greater tendency to differentiate into adipocytes rather than myocytes in cord blood derived

from obese pregnancies; this is correlated with increased adipose tissue measured in the neonate as early as 72 hours of life.²⁶ Maternal obesity may also directly affect the epigenetic regulation of childhood fat mass.²⁷

Aside from maternal obesity, **maternal undernutrition** during pregnancy is also (perhaps counterintuitively) associated with an increased long-term risk of obesity in offspring. Some of the earliest evidence for this effect comes from observational studies following up the life-long health of babies whose mothers were exposed to famine during pregnancy, particularly the Dutch Hunger Winter – a severe famine limited to a specific population and timeframe during 1944. Methylation of several metabolic function-related genes, especially *IGF2*,²⁸ differed from control populations, even up to six decades after the initial famine exposure.

Maternal smoking during pregnancy may also have an important influence on long-term obesity risk in offspring, with a dose-dependent association up to 15 cigarettes daily.²⁹ While complete cessation is ideal, any reduction in the amount of cigarettes may reduce risk of future obesity in the child. The mechanism by which maternal smoking increases the risk of offspring obesity remains unclear, but recent work has shown that alterations in DNA methylation in cord blood are associated with maternal smoking and these alterations can persist into adult life.³⁰ This is a potential mechanism for later metabolic dysregulation and obesity in offspring, which needs further work.

Type II diabetes

In common with risk of future obesity, there is evidence that both maternal undernutrition and overnutrition during pregnancy can lead to the development of type II diabetes in offspring in later life. Individual baseline glucose tolerance is thought to be multifactorial, including a considerable genetic component, but there is strong evidence that epigenetic programming during intrauterine development is an important contributing factor. Multiple mechanisms proposed to be important in developmental programming link the suboptimal intrauterine environment to later type II diabetes risk in both animal models and human cohort studies. The mechanisms include altered DNA methylation patterns,³¹ altered pancreatic beta cell development³² and decreased histone acetylation in the region of the pancreatic islets.³³

Cardiometabolic disorders

Future cardiometabolic risk has also been linked to suboptimal intrauterine environments. In animal models, altered sensitivity to leptin and increased renal nerve sympathetic activity have been observed in the offspring of obese mothers, which may contribute considerably to the later increased risk of both hypertension and diabetes.³⁴ In human cohorts, there is evidence of increased systolic blood

pressure in children exposed to maternal GDM during pregnancy,³⁵ an effect that appears independent of their risk of subsequent obesity.

Appetite and behavioural regulation

Programming of appetite and eating behaviours is a mechanism by which intrauterine development may affect the risk of later metabolic disorders in offspring. Studies in animal models reveal mechanisms by which the developing brain, especially the HPA axis, might influence the intrauterine environment. A key example is the link between maternal obesity and programmed feeding behaviour in offspring. Maternal obesity in rats alters dopaminergic pathways and opioid-related gene expression in the hypothalamus,³⁶ which are important determinants of eating behaviour. Evidence that appetite and eating behaviour can be developmentally programmed in humans comes from studies of pregnancies in type 1 diabetic mothers, where the fetus is exposed to maternal hyperglycaemia. Evidence suggests there are notable changes to leptin expression in adult offspring, which may have a major impact on feeding behaviours and contribute to obesity.³⁷

Dyslipidaemia

There is increasing evidence that dyslipidaemia, a key factor in obesity and future cardiovascular complications, may also be programmed in utero. Both total cholesterol and high-density lipoprotein (HDL) cholesterol levels in infants are linked to epigenetic alterations programmed during early development and may affect their risk of future cardiovascular disease.³⁸ Nonhuman primate studies have shown that offspring born to mothers eating a high-fat diet have increased hepatic triglycerides antenatally. An interesting feature of this study was that offspring continued to have increased triglycerides and increased expression of lipogenic genes at 1 year of age, even after weaning onto a healthy postnatal diet. This demonstrates the importance of early intrauterine development in determining metabolic risk.³⁹

During pregnancy, obese mothers usually have high circulating availability of fatty acids, which can easily cross the placenta. The accumulation of fatty acids in infants born to obese mothers with GDM can be demonstrated via magnetic resonance imaging (MRI) scans. MRI scans show a 70% increase in hepatic adiposity (with no additional increase in subcutaneous or abdominal fat) in infants born to obese mothers with GDM compared with controls.⁴⁰ In utero exposure to additional fatty acids and other metabolites appears to increase the offspring's lifetime risk of developing non-alcoholic fatty liver disease.⁴¹ Further evidence from the Dutch Hunger Winter studies also links maternal undernutrition with an altered lipid profile later in life. Adults who had been exposed to famine while in the womb

were more likely than a similar control population to have dyslipidaemia at age 50.⁴²

Evidence for developmental programming of female reproductive capacity

There is strong evidence of importance of the intrauterine environment in programming later endocrine-metabolic phenotypes in exposed offspring. These outcomes may subsequently influence the likelihood of successful reproduction; for example, obesity and anovulatory infertility are closely linked. One important manifestation of metabolic dysfunction in adult females, which may significantly influence reproductive capacity, is polycystic ovary syndrome (PCOS). PCOS is a heterogeneous syndrome involving hyperandrogenism, oligoanovulation, and characteristic appearances of the ovaries on ultrasound. While there is good evidence for a component of polygenic heritability, there is also human study evidence that the intrauterine environment is important in determining the likelihood of developing PCOS.⁴³ During midtrimester fetal development, the human ovary can already produce an androgenic response to changes in the intrauterine environment, especially in response to maternal hyperinsulinaemia.⁴⁴ Evidence suggests that there are increased testosterone levels in cord blood of female infants born to mothers who themselves have PCOS.⁴⁵ Early exposure to an altered steroid milieu may therefore be an important contributing factor to the risk of developing PCOS and anovulatory infertility in later life.

Ovarian reserve

Compared with endocrine-metabolic phenotypes, ovarian reserve is much more difficult to measure directly in human populations. Hence, much of the work looking at the impact of the intrauterine environment on ovarian reserve has been performed **exclusively using animal models, especially rodents.** Female rats exposed to **suboptimal maternal nutrition in utero⁴⁶ have accelerated decline in their ovarian reserve compared with controls whose mothers ate normal diets throughout pregnancy.** An interesting observation from studies examining the impact of an adverse intrauterine environment on the female reproductive tract is that the developing ovary appears highly sensitive to exposure to suboptimal intrauterine environments. This is observed in rodent models not only following exposure to altered maternal nutrition, but also to developmental hypoxia,⁴⁷ which is one of the commonest adverse intrauterine exposures during human pregnancy worldwide. Studies conducted in several animal models report accelerated oxidative stress and reduction in ovarian telomere length alongside a severe reduction in available ovarian reserve by young adulthood following exposure to a

Table 1. Potential developmental programming factors and suggested management. The possible health risks to offspring are drawn from various human cohort studies.

Maternal factor	Possible risks to later offspring health	Current management strategies
Low body mass index/ underweight	Obesity Hypertension	Correction of any nutrient deficiencies Advice regarding healthy weight maintenance Sensitive exploration of any related disorders, e.g., mental health issues
Obesity	Obesity Dyslipidaemia Cardiovascular disease Type II diabetes	Weight loss and dietary optimisation prior to conception Encourage physical activity Aspirin during pregnancy
Smoking	Obesity Hypertension Insulin resistance	Smoking cessation Aspirin during pregnancy
Chronic fetal hypoxia	Obesity Cardiovascular disease	Close monitoring of pregnancy, including uterine artery dopplers Optimise timing of delivery
Gestational diabetes mellitus	Obesity Impaired glucose tolerance Type II diabetes	Control of diabetes in pregnancy (diet/lifestyle, metformin, insulin) Advice regarding continuing maternal diabetes screening

suboptimal intrauterine environment.⁴⁸ These concerning findings make further investigation of these effects in human cohorts an important priority, notwithstanding the practical difficulties of conducting such studies.

Oviductal programming

Aside from the gonads themselves, altered reproductive function in females can arise from multiple issues with different aspects of the reproductive system. One major cause of infertility in human populations is oviductal problems (tubal factor infertility), which may account for ~30% of all female infertility.⁴⁹ A few studies have investigated whether the developing oviduct might also be vulnerable to developmental programming stresses. Interestingly, **exposure to chronic gestational hypoxia⁵⁰ in animal models appears to adversely influence oviductal development, with consequent accelerated tissue ageing and high levels of oxidative stress.** Available studies suggest that exposure to a suboptimal intrauterine environment limits mitochondrial biogenesis and energy production in the adult oviduct, which has potentially important consequences for tubal motility and gamete transport.⁵⁰ The practical difficulties of such investigations in human cohorts mean these findings are currently limited to animal models, but could lead to new insights into tubal infertility and into methods to improve fertility outcomes after early exposure to difficult womb environments.

Other aspects of reproductive health, such as **pubertal timing,⁵¹ are also closely linked to intrauterine development;**

either directly as a developmental programming effect involving the HPA axis, or via accumulation of excess fat mass in childhood. An important **future area for research** is to determine any developmental programming effects on the uterus, either myometrium or endometrium.

Conclusion

The intrauterine environment is a key modulator of health and disease status throughout life. Mounting evidence suggests that the early life environment, in particular maternal diet during pregnancy, interacts with fetal genetics to influence the structure and function of organs and systems in adult offspring. Here, we have focused primarily on metabolic and reproductive health outcomes. However, various other health conditions (such as cardiovascular disease and immune function) are now thought to have a developmental component in their aetiology.

Awareness of the importance of the intrauterine environment for long-term health is increasingly important as the evidence in this area mounts and as the prevalence of high-risk intrauterine environments is increasing in maternity populations. Although current interventions are limited, obstetricians caring for women with high-risk pregnancies should be aware of the later-life health implications for the fetus. The focus needs to be on preconception care. Optimising maternal weight, encouraging physical activity, improving lipid profile and

smoking cessation prior to pregnancy will improve the intrauterine environment (Table 1). Aspirin may also be helpful in maximising placental function where risk factors are present. Obstetricians may also consider expanding preconception counselling to explain that prepregnancy and pregnancy lifestyle factors can influence offspring health across the life-course.

Children who are the survivors of high-risk pregnancies are at increased risk of adverse metabolic health outcomes and more research is required to determine optimal follow-up. As the mechanisms underlying developmental programming effects become clearer, more specific recommendations about care in later life will become possible. Understanding and prediction of disease risk is an important health care goal, particularly as many metabolic and reproductive health issues can be improved if recognised and managed appropriately.

Future work should build on the current compelling evidence that adverse metabolic health can be transmitted through generations via multiple mechanisms. As further evidence accumulates, our ability to improve life-long health, as well as immediate outcomes for the survivors of high-risk pregnancies, will improve.

Disclosure of interests

There are no conflicts of interest.

Contribution to authorship

SD reviewed the literature and wrote the initial draft. CA conceptualised the article and edited the manuscript. Both authors approved the final version and are accountable for accuracy and integrity of the work.

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