Biological and pathological mechanisms leading to the birth of a small vulnerable newborn

Patricia J Hunter, Toluwalase Awoyemi, Adejumoke I Ayede, R Matthew Chico, Anna L David, Kathryn G Dewey, Christopher P Duggan, Michael Gravett, Andrew J Prendergast, Usha Ramakrishnan, Per Ashorn, Nigel Klein and members of the SVN Steering Committee

UCL Great Ormond Street Institute of Child Health, University College London, London, UK (P J Hunter, PhD, Professor N Klein, MD); Feinberg School of Medicine, Northwestern University, Chicago, IL, USA (T Awoyemi DPhil); Department of Paediatrics, College of Medicine, University of Ibadan and University College Hospital, Ibadan, Nigeria (A I Ayede ScE); Department of Disease Control; Faculty of Infectious & Tropical Diseases; London School of Hygiene & Tropical; London, UK (RM Chico, PhD); Elizabeth Garrett Anderson Institute for Women's Health, University College London, London, UK (Professor A L David, PhD); Department of Nutrition, University of California at Davis, Davis, CA, USA (Professor K G Dewey, PhD); Center for Nutrition, Boston Children's Hospital, Harvard Medical School; Departments of Nutrition and Global Health and Population, Harvard TH Chan School of Public Health; all in Boston, MA, USA, (Professor C P Duggan, MD); Department of Obstetrics & Gynecology, University of Washington, Seattle, WA, USA (Professor M Gravett, MD); Rollins School of Public Health, Emory University, Atlanta, GA, USA (Professor U Ramakrishnan, PhD); Blizard Institute, Queen Mary University of London, London, UK and Zvitambo Institute for Maternal & Child Health Research, Harare, Zimbabwe (Professor A J Prendergast, DPhil); Center for Child, Adolescent, and Maternal Health Research, Faculty of Medicine and Health Technology, Tampere University and Tampere University Hospital, Tampere, Finland, (Professor P Ashorn, MD).

Corresponding author:
Patricia J Hunter, PhD
UCL Great Ormond Street Institute of Child Health
University College London
London, WC1N 1EH, UK
Email: patricia.hunter@ucl.ac.uk

Patricia J Hunter, PhD Great Ormond Street Institute of Child Health University College London London, UK *Email:* patricia.hunter@ucl.ac.uk	**Christopher P Duggan, MD** Center for Nutrition Boston Children's Hospital Harvard Medical School Departments of Nutrition and Global Health and Population Harvard TH Chan School of Public Health Boston, MA, USA *Email:* Christopher.Duggan@childrens.harvard.edu
Toluwalase Awoyemi, DPhil Feinberg School of Medicine Northwestern University Chicago, IL, USA *Email:* toluwalase.awoyemi@northwestern.edu	**Michael Gravett, MD** Departments of Obstetrics & Gynaecology and of Global Health University of Washington Seattle, WA, USA *Email:* gravettm@uw.edu
Adejumoke I Ayede, ScE Department of Paediatrics College of Medicine University of Ibadan And University College Hospital Ibadan, Nigeria *Email:* idayede@yahoo.co.uk	**Andrew J Prendergast, DPhil** Blizard Institute Queen Mary University of London London, UK Zvitambo Institute for Maternal & Child Health Research Harare, Zimbabwe *Email:* a.prendergast@qmul.ac.uk
R Matthew Chico, PhD Department of Disease Control Faculty of Infectious & Tropical Diseases London School of Hygiene & Tropical London, UK *Email:* Matthew.Chico@lshtm.ac.uk	**Usha Ramakrishnan, PhD** Hubert Department of Global Health Rollins School of Public Health Emory University Atlanta, GA, USA *Email*: uramakr@emory.edu
Anna L David, PhD Elizabeth Garrett Anderson Institute for Women's Health University College London London, UK National Institute for Health Research University College London Hospital Biomedical Research Centre London, UK *Email:* a.david@ucl.ac.uk	**Per Ashorn, MD** Center for Child, Adolescent, and Maternal Health Research Faculty of Medicine and Health Technology Tampere University and Tampere University Hospital Tampere, Finland *Email:* per.ashorn@tuni.fi
Kathryn G Dewey, PhD Department of Nutrition University of California, Davis Davis, CA, USA *Email:* kgdewey@ucdavis.edu	**Nigel Klein, MD** Great Ormond Street Institute of Child Health University College London London, UK National Institute for Health Research Great Ormond Street Hospital Biomedical Research Centre London, UK *Email:* n.klein@ucl.ac.uk

Summary

The pathway to a thriving newborn begins pre-conception and continues *in utero* with a healthy placenta and the right balance of nutrients and growth factors that are timed and sequenced alongside hormonal suppression of labour until a mature infant is ready for birth. Optimal nutrition that includes adequate quantities of quality protein, energy, essential fats and an extensive range of vitamins and minerals not only supports fetal growth but may also prevent preterm birth by supporting the immune system and alleviating oxidative stress. Infection, illness, undernourishment, and harmful environmental exposures can alter this trajectory leading to an infant who is too small due to either poor growth during pregnancy or preterm birth. Systemic inflammation suppresses fetal growth by interfering with growth hormone and its regulation of insulin-like growth factors. Evidence supports the prevention and treatment of several maternal infections during pregnancy to improve newborn health. However, microbes, such as *Ureaplasma* species, that are able to ascend the cervix and cause membrane rupture and chorioamnionitis require new strategies for detection and treatment. The surge in fetal cortisol late in pregnancy is essential to parturition at the right time, but acute or chronically high maternal cortisol levels caused by psychological or physical stress may also trigger labour onset prematurely. In every pathway to the small vulnerable newborn, there is a possibility to change direction by supporting improved nutrition, protection against infection, holistic maternal wellness, and healthy environments.

Keywords

Preterm birth, fetal growth restriction, small for gestational age, small vulnerable newborn, pregnancy, nutrition, infection

Key messages

1. Factors that influence fetal growth change over course of pregnancy, from the direct exposure to nutrients in maternal fluids during conception, to the formation and function of the placenta, to the timing of bone elongation and fat deposition. Thus, the timing and regulation of nutrient availability is critical in achieving fetal growth potential.

2. Pregnancy is maintained by the active suppression of labour mechanisms by progesterone and other factors and by a long, closed cervix. Thus, there are physical and chemical "barriers" to the initiation of labour and birth that are overcome by signals that the infant is ready to be born. The barriers can be modulated by progesterone insufficiency, diet and environmental contaminants. In addition, high levels of maternal cortisol and severe inflammation can override the barrier leading to preterm labour and birth.

3. Preterm birth and fetal growth restriction may be the endpoints of different pathways but infection, undernourishment, psychological stress and environmental exposures have the potential to act on both pathways through intermediates of oxidative stress, inflammation, inadequate immune protection and placental dysfunction.

4. New knowledge about the mechanisms of pregnancy continues to emerge providing a better understanding of ways to support optimal fetal growth and duration of gestation targeted to those with the greatest ability to benefit, thus affording opportunities for comprehensive, personalised support for pregnant women globally.

Embedded in the United Nations' Sustainable Development Goals is a roadmap to break the cycle of poverty and disadvantage perpetuated by vulnerable childhood and adolescence giving rise to vulnerable pregnancy and infancy. In this series, we examine the vulnerability conferred by small size at birth resulting from growth restriction and/or preterm birth. We cover the prevalence, causes, consequences and possible routes to prevention, either by accelerating existing strategies or considering new approaches. Approximately one in four infants worldwide is born either preterm, small-for-gestational-age or both.[1] Forty per cent of global neonatal mortality occurs in preterm infants and 28% occurs in small-for-gestational-age infants born at term.[1]

Despite global attention and targets set for reducing the prevalence of the small vulnerable newborn, there has been little change over the last 10 years.[1] The slow progress can be attributed in part to gaps in our common understanding of the mechanisms controlling fetal growth and gestational duration. Multiple, often interacting, risk factors contribute to poor health in women both before and during pregnancy (panel 1). However, connecting risk factors to the biological processes leading to preterm birth and growth restriction remains a challenge. For some of the most prevalent risk factors, the relationship with causal mechanisms may be indirect. For example, maternal iron deficiency anaemia is the largest global population-attributable risk factor for spontaneous preterm and small-for-gestational-age births,[2,3] however iron supplementation (which reduces maternal anaemia by 70%) has not reduced he prevalence of these outcomes in most contexts.[4] A similar conundrum is the global prevalence of bacterial vaginosis and its association with spontaneous preterm birth; 25 years of trials with antibiotics during pregnancy show that treatment can reduce the prevalence of bacterial vaginosis but not the risk of spontaneous preterm birth.[5,6]

Within the series, this article reviews the pathway to the birth of a healthy thriving newborn in order to provide a framework to describe what can go wrong. Knowledge of these mechanisms is incomplete, however new information is constantly emerging, often from disciplines outside of mammalian reproduction and development. Novel concepts emerging from randomised controlled trials, animal models, observational studies and laboratory work that recapitulates mechanisms *in vitro* have enabled connections to be made with biological mechanisms in order to explain why some strategies for prevention are effective and some require new approaches. This article will demonstrate that it is useful to consider preterm birth and growth restriction together because many risk factors can contribute to both, albeit through different pathways. Context-specific, targeted and even personalised intervention strategies to prevent preterm and small-for-gestational-age births are possible and likely to bring better health to the next generation.

Born at the right size but how?

Factors influencing the growth and development of the fetus change over the course of pregnancy. The first critical period begins around the time of conception and ends at implantation. At this stage, the embryo can sense the concentrations of nutrients in the surrounding fluids and calibrate of metabolic processes to compensate for overabundance, in the case of maternal obesity, or paucity, in the case of undernutrition.[7] The subsequent adaptations in embryonic gene expression and regulation can become "fixed" in the form of heritable chromatin changes that can lead to dysregulated fetal growth and obesity and metabolic disease in adulthood.[8]

The next critical period begins with implantation, which triggers a hormonal surge leading to changes in maternal physiology to support placental development and the increased metabolic demands of pregnancy. Fetal trophoblast cells invade the maternal endometrial

spiral arteries, displacing the vascular endothelium and directing larger, stronger versions to be rebuilt on the same tissue scaffold.[9] Proliferating trophoblasts elaborate the basic placental structure, which consists of finger-like villi that float in compartments of maternal blood (Figure 1). Peak placental growth occurs at the end of the first trimester but remodelling of the maternal vasculature continues for the duration of pregnancy (Figure 2).

As the placenta develops, it takes over the production of hormones that maintain pregnancy and direct the production of growth factors (Figure 3). Thus, a physiological dialog ensues between the placenta and fetus, and the placenta and pregnant woman. For example, placentally produced hormones create a transient state of mild insulin resistance at the cellular level in the woman, presumably to free up more glucose for the infant.[10] Excess glucose is taken up and stored as glycogen by the placenta, possibly to buffer the effects of transient moderate undernourishment or to prepare for accelerated weight gain later in gestation.[11]

The second trimester is the critical period of peak fetal length gain, largely driven by insulin-like growth factors (IGFs) and regulated by growth hormone and a system of six binding proteins and their proteases.[12] IGF-1 is involved in bone elongation and skeletal growth.[13] IGF-2 drives placental growth as well as the synthesis of other placentally-derived hormones.[14] The last trimester sees peak fetal weight gain with the enlarging of muscle and laying down of fat under the skin and around the organs. Fat deposition is controlled and regulated by insulin, leptin, adiponectin and other adipokines.[15] Undernutrition during the third trimester leads to an infant that is too thin at birth whereas mid trimester undernutrition leads to an infant that is overall too small.[16] Due to resource allocation to head and brain development (so-called “brain sparing”) head growth can follow a normal growth trajectory even when the growth of the fetal body is faltering.[17] Since maternal weight gain is steadier than that of the infant, it should be possible to identify women who are not gaining adequate

weight and intervene to support nutrient intake ahead of peak fetal weight gain in the third trimester.

Born at the right time

Pregnancy is maintained by progesterone-mediated suppression of the processes of labour and by an impenetrable cervix (Figure 2). Progesterone inhibits the production of components involved in receiving signals to prepare the uterus for labour such as the estrogen and oxytocin receptors. In most mammals, plasma progesterone concentrations decrease towards the end of pregnancy. In contrast, levels remain high throughout human pregnancy, even during labour. Activation of labour systems is brought about instead by the functional inhibition of progesterone, possibly by a soluble "A" form of the progesterone receptor (PR-A).[18]

The uterine cervix remains long and closed for the duration of pregnancy due to its rigid structure bestowed by the high collagen content of the extracellular matrix. Compared with many other mammals, the human cervix needs to be strong enough to counteract the downward pressure of weight attributable to the growing fetus during the time the woman spends in the upright position.[19] Additionally, the cervix needs to be kept free of bacteria ascending from the vagina. Cervical mucus provides a scaffold for immunoglobulins and antimicrobial peptides as it accumulates and forms the mucus plug.[20,21] The cellular defence of the cervix is mainly provided by neutrophils that populate the mucus having exited the maternal circulation.[22]

Events leading to labour and birth of humans are not fully understood. However, there are pathways observed in other mammals that are likely to operate similarly in humans. A

common view is that signals from the infant indicating that key late developmental milestones have been achieved are also able to start the processes leading to labour and birth. For example, one of the final steps in lung development is the release of surfactant to the surface of the lung alveoli so that when they fill with air at birth, the surface tension will be kept low. Since the lungs are full of amniotic fluid and the infant is performing breathing movements in the womb, the surfactant diffuses throughout the amniotic fluid around the infant. In rodents, the accumulation of surfactant in amniotic fluid acts as a trigger to start the birth process.[23,24]

A similar process occurs with fetal cortisol and corticosteroids. Towards the end of pregnancy, the fetal brain signals to increase production of corticotropin releasing hormone which leads to an increase in cortisol and corticosteroids in the fetal circulation (Figure 2).[25] As the main steroid involved in the stress response, cortisol directs the release of glucose into the fetal bloodstream and increases blood flow to the brain. It may have the dual function of bringing new alertness and awareness to the infant as well as signalling that the infant is ready for parturition to begin.

The first committed step toward labour occurs when cortisol and corticosteroids in the fetal circulation reach the threshold for the activation of the production of the cyclooxygenase 2 (COX2) in the fetal membranes (figure 2). COX2 converts long chain polyunsaturated fatty acids (LCPUFAs) into prostaglandins. The essential LCPUFA for labour is arachidonic acid, which selectively accumulates in the myometrium, cervix and fetal membranes over the course of pregnancy.[26] COX2 converts arachidonic acid into prostaglandins E2 and F2α, which trigger a gene and protein expression cascade, leading to the functional inhibition of progesterone, the production of contraction-associated proteins and the recruitment of monocytes and neutrophils to the uterus and cervix.[27] These cells produce matrix

metalloproteinases which dissolve the extracellular collagen matrix of the myometrium and cervix causing the cervix to soften.[28] Tight gap junctions form between the cells of the myometrium, which then takes on the appearance and function of smooth muscle.

Omega-3 LCPUFAs are also substrates of COX2 and may act as competitive inhibitors of prostaglandin E2 and F2a production thus contributing to the maintenance of pregnancy and the inhibition of labour.[29] Women with lower circulating concentration of omega-3 LCPUFAs are at increased risk of preterm birth,[30] suggesting that these compounds, like progesterone, act to raise the threshold for the activation of labour processes. One of the unintended consequences of supplementation with omega-3 LCPUFAs is an increase in the rate of post term birth[31] suggesting that if the threshold is too high, signals from the fetus can't overcome the inhibitory mechanisms and the pregnancy is prolonged.

Good nutrition supports more than just growth

The impact of maternal nutrition before and during pregnancy is now understood to extend well beyond birth and childhood into the life courses of future generations.[7,32] Physiological changes in pregnancy enable women to meet the increased demand for energy, nutrients, and oxygen to supply to the growing fetus (Table 1). However, women who begin a pregnancy before having reached their own biological growth potential due to chronic undernourishment, young age, or both, are at increased risk of being unable to meet these demands. Among underweight women, partitioning of energy and nutrients may result in limited provision to the fetus in favour of maternal requirements for her survival. Thus, it is not surprising that underweight women, who may also have inadequate gestational weight gain, are at higher risk of delivering a small-for-gestational-age infant.[39]

198 Anaemia is a highly prevalent risk factor linked to a wide range of adverse pregnancy
199 outcomes.[40] There are many causes of anaemia unrelated to nutrition including malaria and
200 other infectious/inflammatory conditions. However, iron supplementation during pregnancy
201 independently reduces the prevalence of anaemia, suggesting that iron deficiency is a key
202 contributor.[4] Anaemia, as a measurable risk factor, may also identify women with a wider
203 range of micronutrient deficiencies. Supplementation with a broad range of micronutrients is
204 able to lower the risk of small-for-gestational age births,[41,42] particularly among underweight
205 and anaemic women,[42] in comparison to iron and folic acid alone. This positive effect on
206 growth without the provision of energy is likely conferred by the efficiency gained when
207 multiple metabolic processes are supported simultaneously. Provision of micronutrients may
208 also lower the risk of preterm birth in underweight women.[42] There are many mechanisms
209 that might contribute to this effect listed in Table 2. We will expand on the ability of good
210 nutrition to enhance immune responses and reduce damage caused by oxidative stress.

211 Damage to tissue caused by the accumulation of reactive oxygen species is both a threat to
212 pregnancy and a natural consequence of oxygen regulation in the placenta.[47] Micronutrients
213 with antioxidant properties including vitamins C and E, carotenoids and long-chain
214 polyunsaturated fatty acids (LCPUFAs) can reduce oxidative stress. The body can dismantle
215 reactive oxygen species using enzymes such as superoxide dismutase, glutathione reductase
216 and various peroxidases that can catalyse their binding to antioxidant molecules. However,
217 once an antioxidant is peroxidated, it is removed from tissue leading to increased turnover
218 and reduced bioavailability.[48] The pathway to spontaneous preterm birth caused by oxidative
219 stress may involve the increased turnover of LCPUFAs, particularly docosahexaenoic acid,
220 which, as previously discussed, may act as a natural inhibitor of labour. People who smoke
221 cigarettes carry a higher burden of oxidative damage compared with non-smokers,[49] and have
222 lower levels of endogenous omega-3 LCPUFAs.[50] Thus, it is unsurprising that a trial

comparing omega-3 LCPUFA supplementation with placebo in pregnant women found spontaneous preterm birth reduced by almost one-half in smokers, whereas there was no benefit in non-smokers.[51]

Zinc is an essential co-factor for superoxide dismutase and a wide range of enzymes and transcription factors, and its deficiency is associated with immune dysfunction and increased susceptibility to infection.[52] White blood cells require tenfold more zinc in comparison to red blood cells.[53] In a healthy pregnancy, there is an increase in white blood cell counts, largely due to the 50% increase in neutrophils.[54] As one of the first lines of defence against pathogens, neutrophils are ubiquitous at points of entry into the body. In pregnancy, they are crucial to defending the cervix against ascending infection.[22] Recent evidence supports previously unknown roles for neutrophils in vascular and tissue remodelling.[55] The secretion of matrix metalloproteinases, for which zinc is a cofactor, by neutrophils is likely to be essential for this latter role. Blocking neutrophils,[56] knocking out matrix metalloproteinases,[57] and reducing bioavailable zinc,[58] all have detrimental effects on placentation in mice leading to fetal demise. The roles of neutrophils and zinc in placentation and protection against pathways leading to preterm birth are only just beginning to be understood and represent a new frontier in reproductive biology.

Infectious threats to the fetus

Microbial infections in pregnant women are major contributors to preterm birth, growth restriction, stillbirth and infection in newborns. Screening for and treating infections in pregnant women has well-established positive effects and there is a need for wider coverage for syphilis, chlamydia, gonorrhoea, HIV, and malaria. However, even in parts of the world where the prevalence of these infections is low, the majority of spontaneous preterm birth – that is, preterm birth preceded by labour or preterm pre-labour rupture of membranes – is also

likely to be caused by microbial infection given the high prevalence of chorioamnionitis found in membrane and placenta tissue on histopathological examination.[59-61]

Chorioamnionitis refers to infiltration of the fetal membranes by maternal neutrophils. It is usually asymptomatic during pregnancy and the diagnosis is made after the birth of the infant. Whilst it is presumed to be caused by colonisation by bacteria that ascended the cervix from the vagina, identification of microbes in these tissues is seldom undertaken. When molecular methods are used to detect microbes in fetal membranes, the most common species identified are members of the *Ureaplasma* genus of bacteria.[61-63] Some species of *Ureaplasma* are able to break down antimicrobial defences and exploit natural weaknesses in the immune system that are unmasked by pregnancy in some women. This may explain the association between spontaneous preterm birth and both periodontal disease and urinary tract infections.[64,65] The mouth, the vagina, and the urinary tract are dependent on the same mechanisms (antibodies, antimicrobial peptides and neutrophils) to protect against microbial invasion.

There are three general pathways through which infection could lead to spontaneous preterm birth. First, there are likely unique features of certain bacterial species, as opposed to viruses or parasites, that trigger the expression of COX2 on their invasion of the placenta, fetal membranes or amniotic fluid. Injecting bacteria or bacterial products into the uteri of pregnant mice is the most widely-used method of modelling preterm birth.[66] It could be that COX2 can be upregulated by signalling through molecules, such as toll-like receptors 2 and 4, that specifically recognize certain types of bacteria and bacterial products.[67] Secondly, microbes that are able to ascend the cervix from the vagina could simply damage the fetal membranes causing rupture (figure 5). In this scenario, there may not be inflammation or the

activation of mechanisms that lead to labour. In many cases of preterm pre-labour rupture of membranes, labour does not occur after a sufficient period of time and the infant must be delivered by labour induction or Caesarean section due to loss of amniotic fluid and the concerns regarding the potential for systemic spread of the infection. Finally, high levels of inflammatory cytokines in the placenta and may be able to activate COX2 and the pathways that culminate in labour.[68] This may be an evolutionary adaptation to delivery the infant from an unfavourable environment where the mother's life is under threat.

Inflammation likely suppresses fetal growth by inhibiting the growth hormone/insulin-like growth factor (GH/IGF) axis (Figure 4). In a study comparing maternal plasma, placental, and cord blood levels of IGF-1 and its inhibitory binding proteins in pregnancies with and without placental malaria, IGF-1 levels were reduced by 28% in plasma samples from women with placental malaria and by 25% in their neonates compared with samples from uninfected women.[69] The inhibitory IGF binding protein-1 was elevated in cord blood of neonates with placental malaria.[69]

Clues to the molecular interactions between inflammation and growth factors come from the observation of poor growth in children with systemic inflammation,[70] and elevated inflammation in children with poor growth.[71] A surprising result of treating children with anti-tumour necrosis factor alpha and other anti-cytokine therapeutics for inflammatory conditions was the restoration of normal growth trajectory.[70] Studies in mice indicate that interleukin-6, a key inflammatory cytokine that is elevated in response to infection, may have the ability to directly suppress IGF-1 and growth hormone.[72] The slowing of growth in response to inflammation may be an evolutionary adaptation to promote successful vaginal

297 birth. As the mother's body prepares for labour, the increase in systemic inflammatory
298 cytokines may contribute to the observed slowing of head growth at the end of pregnancy.

299 **Cervical shortening and preterm birth**

300 When a woman's cervix shortens in the course of pregnancy, there is an increased risk of
301 preterm birth. It is not known why this occurs in some women, but it is associated with the
302 premature expression of proteins involved in the recruitment of monocytes and neutrophils
303 which could lead to the premature destruction of collagen and loss of integrity.[73] As a key
304 hormone responsible for maintaining pregnancy, progesterone delivered directly to the cervix
305 via vaginal pessaries, injected intramuscularly (IM) or taken as tablets has been tested in
306 randomized controlled trials to determine its effect on preterm birth. The results of these trials
307 have been controversial and contradictory,[74,75] leading the FDA to withdraw the indication
308 for IM progesterone for the prevention of preterm birth due to lack of efficacy.[76] However, a
309 recent individual patient data meta-analysis revealed that both IM and vaginal progesterone
310 supplementation are more effective at reducing preterm birth in women who have a short
311 cervix (< 25 mm) compared to women with other risk factors, with evidence of benefit in
312 reducing preterm birth before 34 weeks more certain for vaginal progesterone.[77] Serial
313 ultrasound surveillance of cervical length is required to reliably detect cervical shortening,
314 which may preclude the use of cervical monitoring in resource-poor settings. Analysis of
315 soluble factors in amniotic and vaginal fluids have identified macrophage chemoattractant
316 protein 1 as a biomarker with the strongest association with cervical shortening.[73,78,79]
317 Macrophage chemoattractant protein 1 is easy to detect in mucus from the vaginal end of the
318 cervix and holds potential to report cervical shortening with minimal equipment.

319 **Pre-eclampsia, fetal growth restriction and preterm birth**

Major problems arising during implantation and early placental development result in miscarriage. However, minor issues often remain silent until around mid-gestation when the fetus overtakes the placenta in size. At this time, minor inadequacies in placental size, patterning or maternal blood supply can result in an inability to meet the requirements for the growth and development of the fetus. For reasons that are not completely understood, one of the most common signs that there are supply-and-demand issues with a pregnancy is the elevation of the pregnant woman's blood pressure. The clinical definition of pre-eclampsia has recently been expanded to include the development of high blood pressure during pregnancy along with any related problem, not only elevated protein in the urine.[80] Five percent of pregnancies worldwide are affected by pre-eclampsia with 76,000 attributable maternal deaths per year, second only to post-partum haemorrhage as a cause of maternal death. Around 500,000 fetal and newborn deaths each year are attributed to pre-eclampsia and eclampsia.[80] Approximately 9% of all preterm birth is by induction of labour or Caesarean section to treat severe pre-eclampsia and eclampsia.[81]

Pre-existing maternal cardiovascular vulnerability and poor cardiovascular adaptation to pregnancy are increasingly recognised as important to the development of pre-eclampsia.[82] Pregnancy has even been described as a stress-test that reveals women who have poor cardiovascular reserve or dysfunction.[83] It is therefore unsurprising that well-established treatments for cardiovascular disease such as low-dose aspirin, when given during pregnancy, also reduce the risk of preterm pre-eclampsia,[84] and new treatments (statins) are under investigation.[85]

A calcium-rich diet or calcium supplementation during pregnancy are also able to reduce the risk of pre-eclampsia and associated morbidity and mortality in the newborn.[86] It is likely that

both aspirin and calcium are able to prevent the establishment of a systemic vasoconstrictive environment. In chronic, sustained high blood pressure, the ratio of the vasoconstrictive thromboxane to the vasodilator prostacyclin is skewed towards vasoconstriction. Both molecules are synthesized by cyclooxygenases 1 and 2 (COX1/2). At low doses, aspirin appears to be able selectively and irreversibly to inactivate COX1 in platelets, thus reducing thromboxane production and restoring this ratio to normotensive levels.[87] However, aspirin has been shown to be most effective at preventing preterm pre-eclampsia when commenced early in pregnancy (< 16 weeks) suggesting a supportive effect on early placentation.[88]

Changing social and environmental contexts

Some subgroups of pregnant women, such as smokers, primi- and secundigravidae, teenagers, and women with low body mass index scores, tend to respond more favourably to nutrient supplementation or preventive treatment of infections, reducing the risk of delivering small and vulnerable newborns. However, this does not justify the exclusive use of these interventions strategies to reduce the prevalence of small vulnerable newborns. Increased antenatal contacts afford opportunities to address the wellbeing of pregnant women in a more holistic way. Depression, anxiety, lack of agency, chronic illness, physical workload and intimate partner abuse can all be exacerbated by pregnancy. High levels of psychological and physical stress during pregnancy are associated with growth restriction and shorter pregnancy duration.[89-91] Cortisol entering the placenta from the fetal circulation is an important step in the preparation of mother and child for birth. Although increases in cortisol and corticotropin releasing hormone in the mother's circulation are normal during pregnancy, it is possible that prolonged elevated or acute bursts of cortisol may be able to trigger preterm labour. Furthermore, elevated cortisol has also been associated with higher concentrations of

proinflammatory cytokines,[92,93] that can negatively affect fetal growth as previously described (Figure 4).

Creation of energy from oxygen combined with glucose and other monosaccharides is the final step in the pathway that powers fetal growth. The pathway starts with clean air that is free of pollutants that interfere with oxygen binding by maternal hemoglobin. In addition to increasing the burden of oxidative stress, smoking and cooking over biomass fuels can limit oxygen delivery to the placenta (Figure 4).[94] Exposure to air pollution and living at high altitude have also been linked to fetal growth restriction.[95,96] Interventions that help women to quit or reduce smoking during pregnancy reduce the risk of giving birth to a small infant.[97] Countries that have banned smoking in indoor public spaces have experienced a dramatic reduction in the prevalence of preterm and low birth weight newborns.[98-100] Low- and middle-income countries have higher outdoor pollution levels and indoor pollution due to a reliance on solid biomass (usually wood) fuels and chimneyless stoves for cooking and heating.[101] Because women are more exposed to indoor pollution from cookstoves and heating due to a greater amount of time spent in the home, the World Health Organization considers indoor pollution as a "silent killer" of women in low-resource settings.[102] Trials of liquid fuel cookstoves have so far failed to significantly lower the risk of low birth weight, preterm birth or small-for-gestational-age births, potentially through being unable to reduce sufficient airborne particulate matter to have an observable effect.[103,104]

New evidence is emerging on the effect extra heat on pregnancy outcomes, with a 5% (95% CI 3% - 7%) increase in the odds of having a preterm birth every one degrees above seasonal average.[105,106] Further epidemiological evidence suggests that conception and early first trimester are particularly vulnerable to heat stress, increasing the risk of stillbirth and preterm birth.[107] In animals, transient elevated temperatures lead to reduced feeding and overall food

intake resulting in growth restriction in the fetus.[108] However, the damage may run deeper with loss of intestinal barrier function, changes to intestinal epithelial morphology.[109]

Food and water-borne pollutants are also likely to contribute to the prevalence of small vulnerable newborns. Components of Aspergillus fungal spores collectively known as aflatoxins are common contaminants of food production in under-resourced settings.[110] High concentrations of aflatoxins in maternal and cord blood are associated with low birthweight, likely mediated through growth restriction, although the exact mechanism is not known.[111] In addition to known teratogenic and carcinogenic effects of aflatoxins, they may also interfere with hormone secretion and signaling and thus are part of a wider group of both natural and artificial toxicants known as endocrine disruptors, which include bisphenol A, phthalates, pesticides, polychlorinated biphenyls, polybrominated diethyl ethers and dioxins.[112] Of particular concern is the high levels of phthalate metabolites that contaminate food and water globally. In keeping with their role in modulating estrogen levels, different phthalate compounds can increase or reduce gestational length and are therefore associated with both pre- and post-term birth.[113] Governments have sought to ban the use of phthalates in plastics production, however the toxicity of potential replacements is uncertain.[112]

What can be done? The foreground and the horizon

Knowledge of the mechanisms that lead to the birth of a small vulnerable newborn continues to grow as well as our understanding of how to intervene to reduce or prevent this outcome. In the short term, increasing the quantity and quality of antenatal contacts with healthcare providers affords the opportunity to monitor and support physical (weight gain, fetal growth, prevention and treatment of pregnancy complications) and psychological (mental health, agency) wellbeing. Significant reduction in preterm birth and growth restriction can be

419 achieved with broader implementation of proven antenatal interventions, including multiple
420 micronutrient supplements, balanced protein energy supplements, aspirin, treatment of
421 syphilis, education for smoking cessation, prevention of malaria in pregnancy, treatment of
422 asymptomatic bacteriuria, and progesterone provided vaginally as presented with this
423 series.[114] In addition, the specific vulnerability of those *in utero* to poor air quality, heat
424 waves and toxins in food and water should contribute the urgency of global efforts to reduce
425 harmful environmental exposures and the impact of climate change.
426
427 In the longer term, new knowledge can be used to improve our understanding of the
428 molecular and cellular biology underlying risk factors that inform interventions for
429 populations with the greatest ability to benefit. Risk stratification tools and algorithms that
430 incorporate individual risk profiles, together with biomarkers, can identify individuals who
431 might benefit from pre-emptive care and early pathway-specific interventions. For example, a
432 test that predicts future cervical shortening would identify women who are most likely to
433 benefit from progesterone supplementation without the need for serial ultrasound monitoring.
434 Progesterone supplementation itself is also evolving with new analogues that are resistant to
435 inhibition by the mechanisms that lead to labour.[115] Tests that can be performed and
436 interpreted in the timescale of an antenatal care visit (point-of-care tests) will improve uptake
437 of treatment for infections; treatment can be issued on the same day removing the need to
438 return to clinic for follow-up. Point-of-care tests should fulfil the WHO ASSURED
439 (Affordable, Sensitive, Specific, User-friendly, Rapid, and Equipment-free, and Deliverable)
440 criteria for use in low resource settings.[116]
441
442 Placental histopathology is underutilized as a means to diagnose chorioamnionitis and other
443 placental conditions leading to birth of small vulnerable newborns. In cases of preterm pre-

444 labour rupture of membranes, the rupture site is the "scene of the crime" and should be fully
445 investigated. If *Ureaplasma* species are the leading cause of spontaneous preterm birth,
446 prevalence and virulence factors need to be resolved at the level of species. It will be
447 important to demonstrate a causal relationship between species and spontaneous labour and
448 membrane rupture so that antibiotics that can "cure" the individual and prevent these
449 outcomes are not overused.
450
451 There are also new opportunities to understand placental health *in situ*. A particularly
452 promising development is the discovery of extracellular vesicles which are small particles
453 consisting of a lipid bilayer containing the proteins, metabolites, RNA, and DNA that have
454 budded off from a parent cell. In pregnancy, extracellular vesicles in the maternal circulation
455 mainly come from fetal trophoblasts of the placenta.[117] Extracellular vesicles in a peripheral
456 blood may reveal key aspects of the placental environment including oxygen tension, glucose
457 concentration, inflammation, and vascular dysfunction. In abnormal states such as gestational
458 diabetes and pre-eclampsia, numbers of extracellular vesicles are elevated and contain
459 molecular signatures of these conditions.[118]
460
461 Every woman's journey through pregnancy and childbirth is unique and the ultimate goal
462 should be individually tailored care for all with an eye towards optimizing both mother and
463 infant health and wellbeing. Personalized antenatal care does not need to be complex or
464 expensive but the barriers may be higher in low- and middle income settings in comparison
465 with a pragmatic public health approach. Interventions can span from the bedside (e.g., better
466 gestational age assessment) to the clinic (e.g. pre-eclampsia screening) to the operating room
467 (e.g. safer anaesthesia for Caesarean sections) and to society generally (e.g. limiting tobacco
468 or pollution exposure). A more precise deployment of the existing toolkit of interventions is

likely to be more cost effective. However, many aspects of even healthy pregnancy remain poorly understood, and it is only with continuous discovery that we move forward.

Authors' contributions

PA and NK, in collaboration with other members of the Lancet SVN steering committee, designed the study. NK and PJH verified the underlying data and PJH conducted the analyses. All authors participated in the conceptualisation and drafting of the original manuscript, reviewed and edited subsequent drafts, and approved the final version of the manuscript.

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Author collaborative groups

Lancet Small Vulnerable Newborn Steering Committee*:* Per Ashorn, Robert E Black, Joy E Lawn, Ulla Ashorn, Nigel Klein, G Justus Hofmeyr, Marleen Temmerman, Sufia Askari

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Table 1. Changes to organ systems in women during pregnancy.

Organ system	**Change**
Heart	Cardiac output increases by 50%.[33]
Lungs	Ventilation (volume/minute) increases by 50%.[34]
Vasculature	Vascular resistance decreases by 30 – 50%.[33]
Red blood cells	Early 10% decrease in RBC and hemoglobin per volume due to increase in plasma volume. [35]
White blood cells	Circulating neutrophil counts increase by 50%.[36] T cells become less responsive to antigenic stimulation.[37]
Gastro-intestinal tract	Transit time slows down, possibly to allow longer time for absorption of nutrients.[38]
Pancreas	Small increase in insulin production in response to mild insulin resistance in maternal tissues.[10]

Table 2. Nutritional factors related to the small vulnerable newborn

Maternal nutritional factor	Potential mechanistic pathways	Outcomes
Nutrient supply (energy and macronutrients: carbohydrates, proteins, lipids)	Energy and nutrient delivery to the placenta and fetus.[43]	Growth restriction
Body composition (underweight, overweight); gestational weight gain (GWG)	Underweight or low GWG: low energy supply.[32] Overweight or excess GWG: metabolic and hormonal dysregulation, gestational diabetes, hypertension, inflammation.[44]	Growth restriction
Dietary quality	Metabolic and hormonal dysregulation, gestational diabetes, hypertension, inflammation, oxidative stress.	Growth restriction, preterm birth
Stature	Small "container effect" on uterine and placental size.[45]	Growth restriction
Micronutrients related to cardiac function, anaemia and oxygen supply (e.g., iron, riboflavin, folic acid, vitamin B12, vitamin C)	Oxygen supply to placenta and fetus.	Growth restriction, preterm birth
Nutrients that support immune function (e.g., zinc, fatty acids, vitamin D, iron)	Ability to fight infection and control inflammation.	Fetal growth restriction, preterm birth
Antioxidants and cofactors of antioxidant enzymes (e.g., vitamins C, E, carotenoids, copper, zinc, fatty acids)	Ability to reduce and repair damage caused by oxidative stress.	Fetal growth restriction, preterm birth
Nutrients related to cortisol metabolism (e.g., fatty acids, zinc, magnesium)	Control of inflammation, prevention of preterm COX2 activation and prostaglandin production.	Fetal growth restriction, preterm birth
Nutrients related to mitochondrial function (e.g., vitamins C and E, zinc, copper, iodine, selenium)	Mitochondrial efficiency and protection against oxidative stress.[46]	Fetal growth restriction
Nutrients related to production of prostaglandins (e.g., long chain poly-unsaturated fatty acids)	Omega-3 fatty acids: competitive inhibition of preterm production of prostaglandins E2 and F2α from arachidonic acid.[29]	Preterm birth

Panel 1. Risk factors for the birth of a small vulnerable newborn

Undernourishment	**Infection**	**Characteristics of woman and pregnancy**	**Environmental exposures and psychosocial stress**
Anaemia	HIV	First pregnancy	Unwanted pregnancy
Zinc deficiency	Malaria	Adolescent pregnancy	Intimate partner abuse
Calcium deficiency	Syphilis	Short interpregnancy interval	Lack of support or agency
Short stature	Chlamydia	Extreme parity	Mental illness
Low BMI	Gonorrhoea	Older age	Smoking
Inadequate weight gain	Urinary tract infection	Preeclampsia	Alcohol abuse
	Bacterial vaginosis	Placental dysfunction	Drug abuse
	Trichomonas vaginalis	Gestational diabetes	Toxins
	Group B Streptococcus	Hypothyroidism	Endocrine disruptors
		Cervical weakness	Indoor air pollution
		Uterine malformations	Outdoor air pollution
		Endometriosis	Heat waves
		Multiple pregnancy	High altitude

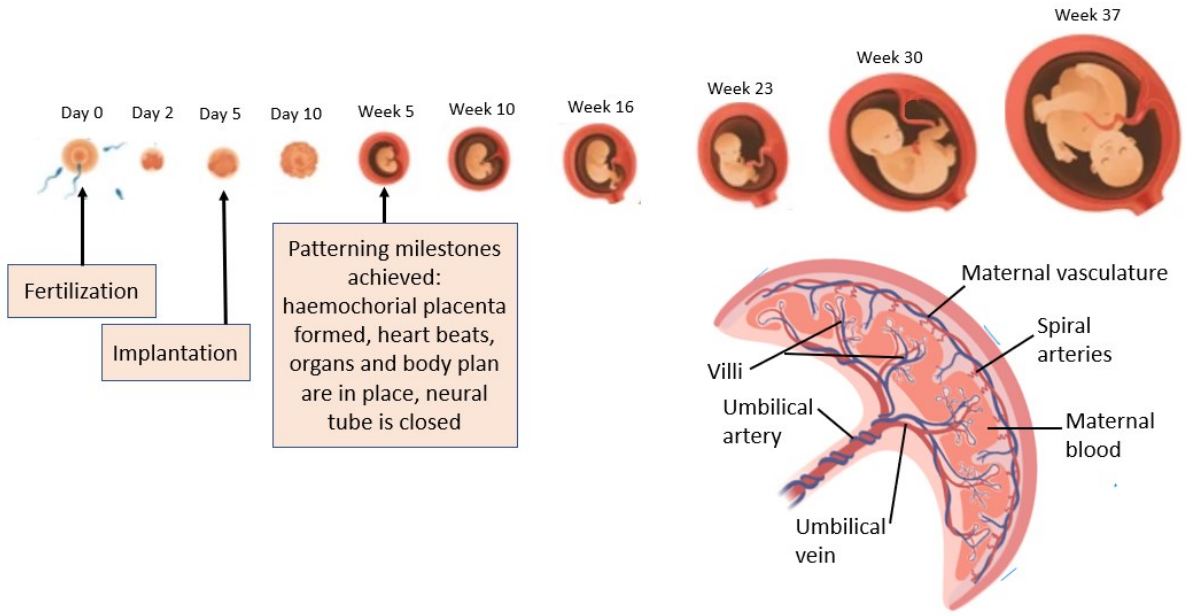


Figure 1. Developing fetus and fully developed placenta. The basic body plan with rudimentary organs are in place by 5 weeks post fertilization. The umbilical artery carries deoxygenated, waste-replete, nutrient-depleted fetal blood to the placental villi where waste is exchanged for nutrients and carbon dioxide is exchanged for oxygen from maternal blood.

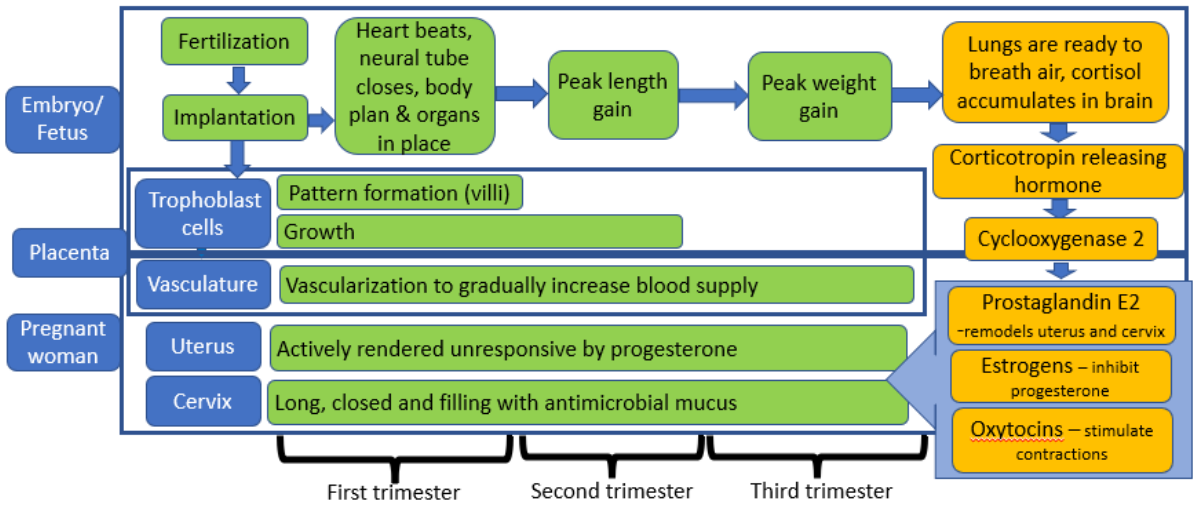


Figure 2. Conceptual model of key determinants of gestational length. When the fetus is ready to be born, cortisol enters the placenta and circulation and activates cyclooxygenase-2 to generate prostaglandin E2, which directs cervical and uterine remodelling. Estrogens override the suppressive effects of progesterone and oxytocins trigger uterine contractions. CRH – corticotropin releasing hormone.

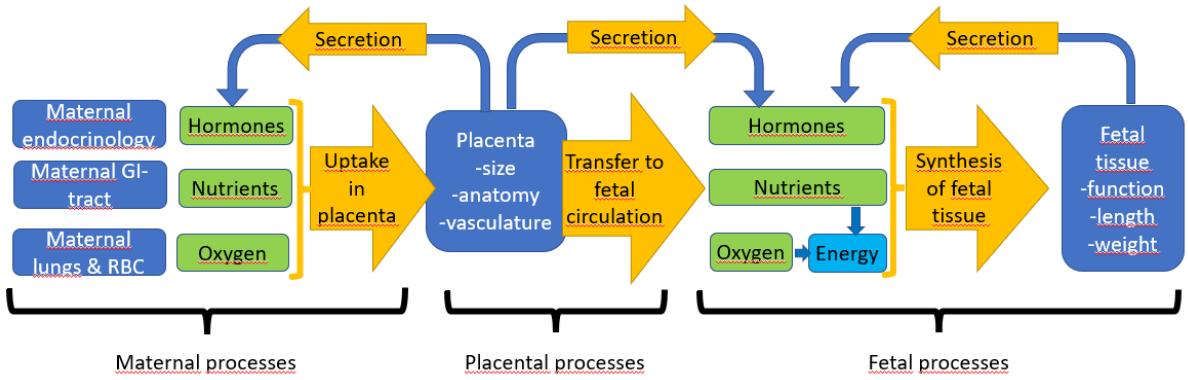
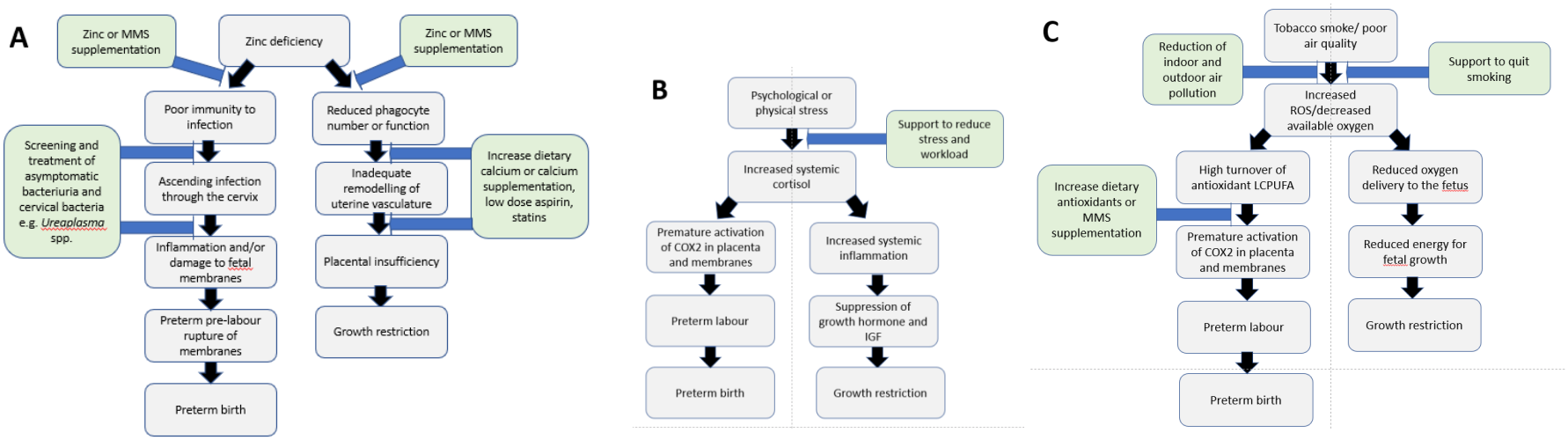


Figure 3. Conceptual model of key determinants of fetal growth. Hormones, nutrients and oxygen from the mother are taken up by the placenta and transferred to the fetal circulation to support synthesis of fetal tissue.



2

3 Figure 4. Examples of exposures that are able to contribute to both preterm birth and growth restriction via different pathways and ways to
4 intervene toward prevention. Zinc deficiency (A), psychological and physical stress (B) and poor air quality/tobacco smoke (C) contribute to the
5 birth of a small vulnerable newborn. MMS – multiple micronutrient supplements, COX2 - cyclooxygenase 2, LCPUFA – long chain
6 polyunsaturated fatty acids, IGF – insulin-like growth factor, ROS – reactive oxygen species.

7

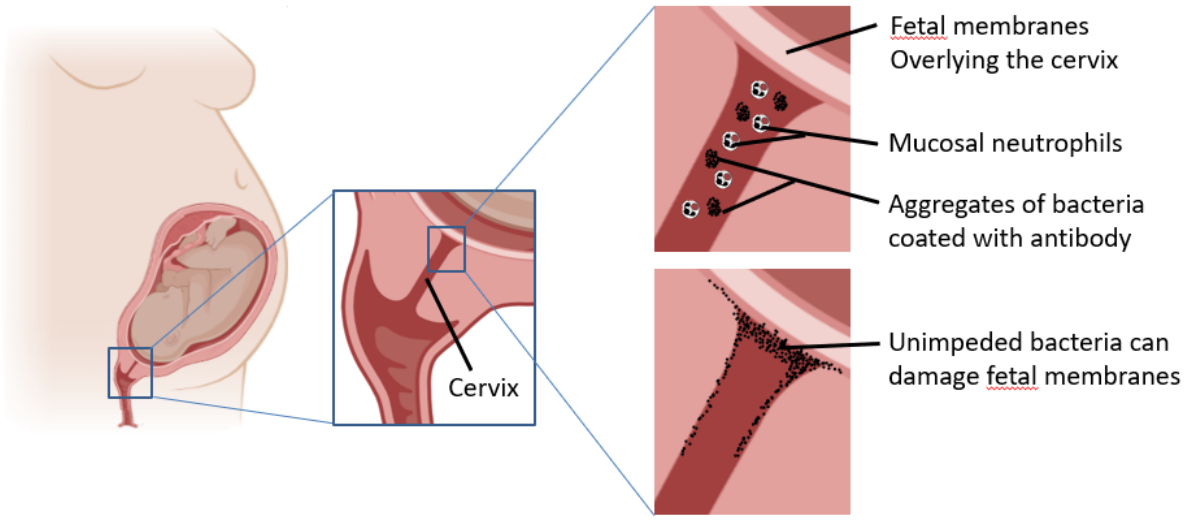


Figure 5. Immune defence of the cervix. The cervix remains long and closed for the duration of pregnancy. It is defended by antimicrobial chemicals including peptides, antibodies and enzymes. Neutrophils are also present in the mucus and are able to destroy invading microbes. In the absence of adequate immune defence, bacteria are able to colonize and damage the membranes leading to rupture or chorioamnionitis.