

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

Patricia J Hunter, Toluwalase Awoyemi, Adejumo 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 MSc); 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

<p>Patricia J Hunter, PhD Great Ormond Street Institute of Child Health University College London London, UK <i>Email:</i> patricia.hunter@ucl.ac.uk</p>	<p>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 <i>Email:</i> Christopher.Duggan@childrens.harvard.edu</p>
<p>Toluwalase Awoyemi, DPhil Feinberg School of Medicine Northwestern University Chicago, IL, USA <i>Email:</i> toluwalase.awoyemi@northwestern.edu</p>	<p>Michael Gravett, MD Departments of Obstetrics & Gynaecology and of Global Health University of Washington Seattle, WA, USA <i>Email:</i> gravetm@uw.edu</p>
<p>Adejumoke I Ayede, MSc Department of Paediatrics College of Medicine University of Ibadan And University College Hospital Ibadan, Nigeria <i>Email:</i> idayede@yahoo.co.uk</p>	<p>Andrew J Prendergast, DPhil Blizard Institute Queen Mary University of London London, UK Zvitambo Institute for Maternal & Child Health Research Harare, Zimbabwe <i>Email:</i> a.prendergast@qmul.ac.uk</p>
<p>R Matthew Chico, PhD Department of Disease Control Faculty of Infectious & Tropical Diseases London School of Hygiene & Tropical London, UK <i>Email:</i> Matthew.Chico@lshtm.ac.uk</p>	<p>Usha Ramakrishnan, PhD Hubert Department of Global Health Rollins School of Public Health Emory University Atlanta, GA, USA <i>Email:</i> uramakr@emory.edu</p>
<p>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 <i>Email:</i> a.david@ucl.ac.uk</p>	<p>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 <i>Email:</i> per.ashorn@tuni.fi</p>
<p>Kathryn G Dewey, PhD Department of Nutrition University of California, Davis Davis, CA, USA <i>Email:</i> kgdewey@ucdavis.edu</p>	<p>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 <i>Email:</i> n.klein@ucl.ac.uk</p>

1 **Summary**

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

20 **Keywords**

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

23

24

25 Key messages

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

31
32 2. Pregnancy is maintained by the active suppression of labour mechanisms by
33 progesterone and other factors and by a long, closed cervix. Thus, there are physical
34 and chemical “barriers” to the initiation of labour and birth that are overcome by
35 signals that the infant is ready to be born. The barriers can be modulated by
36 progesterone insufficiency, diet and environmental contaminants. In addition, high
37 levels of maternal cortisol and severe inflammation can override the barrier leading to
38 preterm labour and birth.

39
40 3. Preterm birth and fetal growth restriction may be the endpoints of different pathways
41 but infection, undernourishment, psychological stress and environmental exposures
42 have the potential to act on both pathways through intermediates of oxidative stress,
43 inflammation, inadequate immune protection and placental dysfunction.

44
45 4. New knowledge about the mechanisms of pregnancy continues to emerge providing a
46 better understanding of ways to support optimal fetal growth and duration of gestation
47 targeted to those with the greatest ability to benefit, thus affording opportunities for
48 comprehensive, personalised support for pregnant women globally.

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

58

59 Despite global attention and targets set for reducing the prevalence of the small vulnerable
60 newborn, there has been little change over the last 10 years.¹ The slow progress can be
61 attributed in part to gaps in our common understanding of the mechanisms controlling fetal
62 growth and gestational duration. Multiple, often interacting, risk factors contribute to poor
63 health in women both before and during pregnancy (Panel 1). However, connecting risk
64 factors to the biological processes leading to preterm birth and growth restriction remains a
65 challenge. For some of the most prevalent risk factors, the relationship with causal
66 mechanisms may be indirect. For example, maternal iron deficiency anaemia is the largest
67 global population-attributable risk factor for spontaneous preterm and small-for-gestational-
68 age births,^{40,41} however iron supplementation (which reduces maternal anaemia by 70%) has
69 not reduced the prevalence of these outcomes in most contexts.⁴² A similar conundrum is the
70 global prevalence of bacterial vaginosis and its association with spontaneous preterm birth;
71 25 years of trials with antibiotics during pregnancy show that treatment can reduce the
72 prevalence of bacterial vaginosis but not the risk of spontaneous preterm birth.^{43,44}

73

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

86

87 **Born at the right size but how?**

88 Factors influencing the growth and development of the fetus change over the course of
89 pregnancy. The first critical period begins around the time of conception and ends at
90 implantation. At this stage, the embryo can sense the concentrations of nutrients in the
91 surrounding fluids and calibrate of metabolic processes to compensate for overabundance, in
92 the case of maternal obesity, or paucity, in the case of undernutrition.⁴⁵ The subsequent
93 adaptations in embryonic gene expression and regulation can become “fixed” in the form of
94 heritable chromatin changes that can lead to dysregulated fetal growth and obesity and
95 metabolic disease in adulthood.⁴⁶

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

99 spiral arteries, displacing the vascular endothelium and directing larger, stronger versions to
100 be rebuilt on the same tissue scaffold.⁴⁷ Proliferating trophoblasts elaborate the basic
101 placental structure, which consists of finger-like villi that float in compartments of maternal
102 blood (Figure 1). Peak placental growth occurs at the end of the first trimester but
103 remodelling of the maternal vasculature continues for the duration of pregnancy (Figure 2).
104 As the placenta develops, it takes over the production of hormones that maintain pregnancy
105 and direct the production of growth factors (Figure 3). Thus, a physiological dialog ensues
106 between the placenta and fetus, and the placenta and pregnant woman. For example,
107 placentally produced hormones create a transient state of mild insulin resistance at the
108 cellular level in the woman, presumably to free up more glucose for the infant.⁴⁸ Excess
109 glucose is taken up and stored as glycogen by the placenta, possibly to buffer the effects of
110 transient moderate undernourishment or to prepare for accelerated weight gain later in
111 gestation.⁴⁹

112 The second trimester is the critical period of peak fetal length gain, largely driven by insulin-
113 like growth factors (IGFs) and regulated by growth hormone and a system of six binding
114 proteins and their proteases.⁵⁰ IGF-1 is involved in bone elongation and skeletal growth.⁵¹
115 IGF-2 drives placental growth as well as the synthesis of other placentally-derived
116 hormones.⁵² The last trimester sees peak fetal weight gain with the enlarging of muscle and
117 laying down of fat under the skin and around the organs. Fat deposition is controlled and
118 regulated by insulin, leptin, adiponectin and other adipokines.⁵³ Undernutrition during the
119 third trimester leads to an infant that is too thin at birth whereas mid trimester undernutrition
120 leads to an infant that is overall too small.⁵⁴ Due to resource allocation to head and brain
121 development (so-called “brain sparing”) head growth can follow a normal growth trajectory
122 even when the growth of the fetal body is faltering.⁵⁵ Since maternal weight gain is steadier
123 than that of the infant, it should be possible to identify women who are not gaining adequate

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

126

127 **Born at the right time**

128 Pregnancy is maintained by progesterone-mediated suppression of the processes of labour
129 and by an impenetrable cervix (Figure 2). Progesterone inhibits the production of components
130 involved in receiving signals to prepare the uterus for labour such as the estrogen and
131 oxytocin receptors. In most mammals, plasma progesterone concentrations decrease towards
132 the end of pregnancy. In contrast, levels remain high throughout human pregnancy, even
133 during labour. Activation of labour systems is brought about instead by the functional
134 inhibition of progesterone, possibly by a soluble “A” form of the progesterone receptor (PR-
135 A).⁵⁶

136

137 The uterine cervix remains long and closed for the duration of pregnancy due to its rigid
138 structure bestowed by the high collagen content of the extracellular matrix. Compared with
139 many other mammals, the human cervix needs to be strong enough to counteract the
140 downward pressure of weight attributable to the growing fetus during the time the woman
141 spends in the upright position.⁵⁷ Additionally, the cervix needs to be kept free of bacteria
142 ascending from the vagina. Cervical mucus provides a scaffold for immunoglobulins and
143 antimicrobial peptides as it accumulates and forms the mucus plug.^{58,59} The cellular defence
144 of the cervix is mainly provided by neutrophils that populate the mucus having exited the
145 maternal circulation.⁶⁰

146

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

149 common view is that signals from the infant indicating that key late developmental
150 milestones have been achieved are also able to start the processes leading to labour and birth.
151 For example, one of the final steps in lung development is the release of surfactant to the
152 surface of the lung alveoli so that when they fill with air at birth, the surface tension will be
153 kept low. Since the lungs are full of amniotic fluid and the infant is performing breathing
154 movements in the womb, the surfactant diffuses throughout the amniotic fluid around the
155 infant. In rodents, the accumulation of surfactant in amniotic fluid acts as a trigger to start the
156 birth process.^{61,62}

157 A similar process occurs with fetal cortisol and corticosteroids. Towards the end of
158 pregnancy, the fetal brain signals to increase production of corticotropin releasing hormone
159 which leads to an increase in cortisol and corticosteroids in the fetal circulation (Figure 2).⁶³
160 As the main steroid involved in the stress response, cortisol directs the release of glucose into
161 the fetal bloodstream and increases blood flow to the brain. It may have the dual function of
162 bringing new alertness and awareness to the infant as well as signalling that the infant is
163 ready for parturition to begin.

164

165 The first committed step toward labour occurs when cortisol and corticosteroids in the fetal
166 circulation reach the threshold for the activation of the production of the cyclooxygenase 2
167 (COX2) in the fetal membranes (figure 2). COX2 converts long chain polyunsaturated fatty
168 acids (LCPUFAs) into prostaglandins. The essential LCPUFA for labour is arachidonic acid,
169 which selectively accumulates in the myometrium, cervix and fetal membranes over the
170 course of pregnancy.⁶⁴ COX2 converts arachidonic acid into prostaglandins E2 and F2 α ,
171 which trigger a gene and protein expression cascade, leading to the functional inhibition of
172 progesterone, the production of contraction-associated proteins and the recruitment of
173 monocytes and neutrophils to the uterus and cervix.⁶⁵ These cells produce matrix

174 metalloproteinases which dissolve the extracellular collagen matrix of the myometrium and
175 cervix causing the cervix to soften.⁶⁶ Tight gap junctions form between the cells of the
176 myometrium, which then takes on the appearance and function of smooth muscle.

177

178 Omega-3 LCPUFAs are also substrates of COX2 and may act as competitive inhibitors of
179 prostaglandin E2 and F2 α production thus contributing to the maintenance of pregnancy and
180 the inhibition of labour.⁶⁷ Women with lower circulating concentration of omega-3
181 LCPUFAs are at increased risk of preterm birth,⁶⁸ suggesting that these compounds, like
182 progesterone, act to raise the threshold for the activation of labour processes. One of the
183 unintended consequences of supplementation with omega-3 LCPUFAs is an increase in the
184 rate of post term birth⁶⁹ suggesting that if the threshold is too high, signals from the fetus
185 can't overcome the inhibitory mechanisms and the pregnancy is prolonged.

186

187 **Good nutrition supports more than just growth**

188 The impact of maternal nutrition before and during pregnancy is now understood to extend
189 well beyond birth and childhood into the life courses of future generations.^{45,70} Physiological
190 changes in pregnancy enable women to meet the increased demand for energy, nutrients, and
191 oxygen to supply to the growing fetus (Table 1). However, women who begin a pregnancy
192 before having reached their own biological growth potential due to chronic
193 undernourishment, young age, or both, are at increased risk of being unable to meet these
194 demands. Among underweight women, partitioning of energy and nutrients may result in
195 limited provision to the fetus in favour of maternal requirements for her survival. Thus, it is
196 not surprising that underweight women, who may also have inadequate gestational weight
197 gain, are at higher risk of delivering a small-for-gestational-age infant.^{7,77}

198 Anaemia is a highly prevalent risk factor linked to a wide range of adverse pregnancy
199 outcomes.⁷⁸ 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.⁴² 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,^{79,80} particularly among underweight
205 and anaemic women,⁸⁰ 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.⁸¹ 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.⁸⁵ 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.⁸⁶ 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,⁸⁷ and have
222 lower levels of endogenous omega-3 LCPUFAs.⁸⁸ Thus, it is unsurprising that a trial

223 comparing omega-3 LCPUFA supplementation with placebo in pregnant women found
224 spontaneous preterm birth reduced by almost one-half in smokers, whereas there was no
225 benefit in non-smokers.⁸⁹

226 Zinc is an essential co-factor for superoxide dismutase and a wide range of enzymes and
227 transcription factors, and its deficiency is associated with immune dysfunction and increased
228 susceptibility to infection.⁹⁰ White blood cells require tenfold more zinc in comparison to red
229 blood cells.⁹¹ In a healthy pregnancy, there is an increase in white blood cell counts, largely
230 due to the 50% increase in neutrophils.⁷⁴ As one of the first lines of defence against
231 pathogens, neutrophils are ubiquitous at points of entry into the body. In pregnancy, they are
232 crucial to defending the cervix against ascending infection.⁶⁰ Recent evidence supports
233 previously unknown roles for neutrophils in vascular and tissue remodelling.⁹² The secretion
234 of matrix metalloproteinases, for which zinc is a cofactor, by neutrophils is likely to be
235 essential for this latter role. Blocking neutrophils,⁹³ knocking out matrix metalloproteinases,⁹⁴
236 and reducing bioavailable zinc,⁹⁵ all have detrimental effects on placentation in mice leading
237 to fetal demise. The roles of neutrophils and zinc in placentation and protection against
238 pathways leading to preterm birth are only just beginning to be understood and represent a
239 new frontier in reproductive biology.

240

241 **Infectious threats to the fetus**

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

248 likely to be caused by microbial infection given the high prevalence of chorioamnionitis
249 found in membrane and placenta tissue on histopathological examination.⁹⁶⁻⁹⁸
250
251 Chorioamnionitis refers to infiltration of the fetal membranes by maternal neutrophils. It is
252 usually asymptomatic during pregnancy and the diagnosis is made after the birth of the
253 infant. Whilst it is presumed to be caused by colonisation by bacteria that ascended the cervix
254 from the vagina, identification of microbes in these tissues is seldom undertaken. When
255 molecular methods are used to detect microbes in fetal membranes, the most common species
256 identified are members of the *Ureaplasma* genus of bacteria.⁹⁹⁻¹⁰¹ Some species of
257 *Ureaplasma* are able to break down antimicrobial defences and exploit natural weaknesses in
258 the immune system that are unmasked by pregnancy in some women. This may explain the
259 association between spontaneous preterm birth and both periodontal disease and urinary tract
260 infections.^{13,102} The mouth, the vagina, and the urinary tract are dependent on the same
261 mechanisms (antibodies, antimicrobial peptides and neutrophils) to protect against microbial
262 invasion.
263
264 There are three general pathways through which infection could lead to spontaneous preterm
265 birth. First, there are likely unique features of certain bacterial species, as opposed to viruses
266 or parasites, that trigger the expression of COX2 on their invasion of the placenta, fetal
267 membranes or amniotic fluid. Injecting bacteria or bacterial products into the uteri of
268 pregnant mice is the most widely-used method of modelling preterm birth.¹⁰³ It could be that
269 COX2 can be upregulated by signalling through molecules, such as toll-like receptors 2 and
270 4, that specifically recognize certain types of bacteria and bacterial products.¹⁰⁴ Secondly,
271 microbes that are able to ascend the cervix from the vagina could simply damage the fetal
272 membranes causing rupture (Figure 5). In this scenario, there may not be inflammation or the

273 activation of mechanisms that lead to labour. In many cases of preterm pre-labour rupture of
274 membranes, labour does not occur after a sufficient period of time and the infant must be
275 delivered by labour induction or Caesarean section due to loss of amniotic fluid and the
276 concerns regarding the potential for systemic spread of the infection. Finally, high levels of
277 inflammatory cytokines in the placenta and may be able to activate COX2 and the pathways
278 that culminate in labour.¹⁰⁵ This may be an evolutionary adaptation to delivery the infant from
279 an unfavourable environment where the mother's life is under threat.

280

281 Inflammation likely suppresses fetal growth by inhibiting the growth hormone/insulin-like
282 growth factor (GH/IGF) axis (Figure 4). In a study comparing maternal plasma, placental,
283 and cord blood levels of IGF-1 and its inhibitory binding proteins in pregnancies with and
284 without placental malaria, IGF-1 levels were reduced by 28% in plasma samples from women
285 with placental malaria and by 25% in their neonates compared with samples from uninfected
286 women.¹⁰⁶ The inhibitory IGF binding protein-1 was elevated in cord blood of neonates with
287 placental malaria.¹⁰⁶

288

289 Clues to the molecular interactions between inflammation and growth factors come from the
290 observation of poor growth in children with systemic inflammation,¹⁰⁷ and elevated
291 inflammation in children with poor growth.¹⁰⁸ A surprising result of treating children with
292 anti-tumour necrosis factor alpha and other anti-cytokine therapeutics for inflammatory
293 conditions was the restoration of normal growth trajectory.¹⁰⁷ Studies in mice indicate that
294 interleukin-6, a key inflammatory cytokine that is elevated in response to infection, may have
295 the ability to directly suppress IGF-1 and growth hormone.¹⁰⁹ The slowing of growth in
296 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.¹¹⁰ As a key
304 hormone responsible for maintaining pregnancy, progesterone may be able to disrupt this
305 process. Progesterone delivered directly to the cervix in soluble capsules, injected
306 intramuscularly (IM) or taken as tablets has been tested in randomized controlled trials to
307 determine its effect on preterm birth. A recent individual patient data meta-analysis revealed
308 that both vaginal (9 trials, 3769 women) and oral (2 trials, 183 women) progesterone
309 supplementation are effective at reducing preterm birth before 34 weeks of gestation in high
310 risk women, namely those with a previous preterm birth or a short cervix (< 25 mm).¹¹¹
311 The evidence of benefit in reducing birth before 34 weeks is less certain for IM progesterone
312 (5 trials, 3053 women).¹¹¹ Furthermore, there have been recent concerns about the maternal
313 and neonatal safety of the synthetic version of progesterone (17-hydroxyprogesterone
314 caproate) used for IM administration.¹¹² In light of this data, vaginal progesterone remains the
315 most promising treatment to prolong gestation for women with a short cervix.

316 Serial ultrasound surveillance of cervical length is required to reliably detect cervical
317 shortening, which may preclude the use of cervical monitoring in resource-poor settings.
318 Analysis of soluble factors in amniotic and vaginal fluids have identified macrophage
319 chemoattractant protein as a biomarker with the strongest association with cervical
320 shortening.^{110,113,114} Macrophage chemoattractant protein 1 is easy to detect in mucus from

321 the vaginal end of the cervix and holds potential to report cervical shortening with minimal
322 equipment.

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

324 Major problems arising during implantation and early placental development result in
325 miscarriage. However, minor issues often remain silent until around mid-gestation when the
326 fetus overtakes the placenta in size. At this time, minor inadequacies in placental size,
327 patterning or maternal blood supply can result in an inability to meet the requirements for the
328 growth and development of the fetus. For reasons that are not completely understood, one of
329 the most common signs that there are supply-and-demand issues with a pregnancy is the
330 elevation of the pregnant woman's blood pressure. The clinical definition of pre-eclampsia
331 has recently been expanded to include the development of high blood pressure during
332 pregnancy along with any related problem, not only elevated protein in the urine.¹¹⁵ Five
333 percent of pregnancies worldwide are affected by pre-eclampsia with 76,000 attributable
334 maternal deaths per year, second only to post-partum haemorrhage as a cause of maternal
335 death. Around 500,000 fetal and newborn deaths each year are attributed to pre-eclampsia
336 and eclampsia.¹¹⁵ Approximately 9% of all preterm birth is by induction of labour or
337 Caesarean section to treat severe pre-eclampsia and eclampsia.¹⁹

338

339 Pre-existing maternal cardiovascular vulnerability and poor cardiovascular adaptation to
340 pregnancy are increasingly recognised as important to the development of pre-eclampsia.¹¹⁶
341 Pregnancy has even been described as a stress-test that reveals women who have poor
342 cardiovascular reserve or dysfunction.¹¹⁷ It is therefore unsurprising that well-established
343 treatments for cardiovascular disease such as low-dose aspirin, when given during pregnancy,
344 also reduce the risk of preterm pre-eclampsia,¹¹⁸ and new treatments (statins) are under
345 investigation.¹¹⁹

346

347 A calcium-rich diet or calcium supplementation during pregnancy are also able to reduce the
348 risk of pre-eclampsia and associated morbidity and mortality in the newborn.⁴ It is likely that
349 both aspirin and calcium are able to prevent the establishment of a systemic vasoconstrictive
350 environment. In chronic, sustained high blood pressure, the ratio of the vasoconstrictive
351 thromboxane to the vasodilator prostacyclin is skewed towards vasoconstriction. Both
352 molecules are synthesized by cyclooxygenases 1 and 2 (COX1/2). At low doses, aspirin
353 appears to be able selectively and irreversibly to inactivate COX1 in platelets, thus reducing
354 thromboxane production and restoring this ratio to normotensive levels.¹²⁰ However, aspirin
355 has been shown to be most effective at preventing preterm pre-eclampsia when commenced
356 early in pregnancy (< 16 weeks) suggesting a supportive effect on early placentation.¹²¹

357

358 **Changing social and environmental contexts**

359 Some subgroups of pregnant women, such as smokers, primi- and secundigravidae,
360 teenagers, and women with low body mass index scores, tend to respond more favourably to
361 nutrient supplementation or preventive treatment of infections, reducing the risk of delivering
362 small and vulnerable newborns. However, this does not justify the exclusive use of these
363 interventions strategies to reduce the prevalence of small vulnerable newborns. Increased
364 antenatal contacts afford opportunities to address the wellbeing of pregnant women in a more
365 holistic way. Depression, anxiety, lack of agency, chronic illness, physical workload and
366 intimate partner abuse can all be exacerbated by pregnancy. High levels of psychological and
367 physical stress during pregnancy are associated with growth restriction and shorter pregnancy
368 duration.¹²²⁻¹²⁴ Cortisol entering the placenta from the fetal circulation is an important step in
369 the preparation of mother and child for birth. Although increases in cortisol and corticotropin
370 releasing hormone in the mother's circulation are normal during pregnancy, it is possible that

371 prolonged elevated or acute bursts of cortisol may be able to trigger preterm labour.

372 Furthermore, elevated cortisol has also been associated with higher concentrations of

373 proinflammatory cytokines,^{125,126} that can negatively affect fetal growth as previously

374 described (Figure 4).

375

376 Creation of energy from oxygen combined with glucose and other monosaccharides is the

377 final step in the pathway that powers fetal growth. The pathway starts with clean air that is

378 free of pollutants that interfere with oxygen binding by maternal hemoglobin. In addition to

379 increasing the burden of oxidative stress, smoking and cooking over biomass fuels can limit

380 oxygen delivery to the placenta (Figure 4).¹²⁷ Exposure to air pollution and living at high

381 altitude have also been linked to fetal growth restriction.^{128,129} Interventions that help women

382 to quit or reduce smoking during pregnancy reduce the risk of giving birth to a small

383 infant.¹³⁰ Countries that have banned smoking in indoor public spaces have experienced a

384 dramatic reduction in the prevalence of preterm and low birth weight newborns.¹³¹⁻¹³³ Low-

385 and middle-income countries have higher outdoor pollution levels and indoor pollution due to

386 a reliance on solid biomass (usually wood) fuels and chimneyless stoves for cooking and

387 heating.¹³⁴ Because women are more exposed to indoor pollution from cookstoves and

388 heating due to a greater amount of time spent in the home, the World Health Organization

389 considers indoor pollution as a “silent killer” of women in low-resource settings.¹³⁵ Trials of

390 liquid fuel cookstoves have so far failed to demonstrate their ability to lower the risk of low

391 birth weight, preterm birth or small-for-gestational-age births, possibly because they are

392 unable to sufficiently reduce airborne particulate matter to have an observable effect.^{136,137}

393

394 New evidence is emerging on the effect extra heat on pregnancy outcomes, with a 5% (95%

395 CI 3% - 7%) increase in the odds of having a preterm birth every one degrees above seasonal

396 average.^{38,138} Further epidemiological evidence suggests that conception and early first
397 trimester are particularly vulnerable to heat stress, increasing the risk of stillbirth and preterm
398 birth.¹³⁹ In animals, transient elevated temperatures lead to reduced feeding and overall food
399 intake resulting in growth restriction in the fetus.¹⁴⁰ However, the damage may run deeper
400 with loss of intestinal barrier function, changes to intestinal epithelial morphology.¹⁴¹

401
402 Food and water-borne pollutants are also likely to contribute to the prevalence of small
403 vulnerable newborns. Components of *Aspergillus* fungal spores collectively known as
404 aflatoxins are common contaminants of food production in under-resourced settings.¹⁴² High
405 concentrations of aflatoxins in maternal and cord blood are associated with low birthweight,
406 likely mediated through growth restriction, although the exact mechanism is not known.³⁴ In
407 addition to known teratogenic and carcinogenic effects of aflatoxins, they may also interfere
408 with hormone secretion and signaling and thus are part of a wider group of both natural and
409 artificial toxicants known as endocrine disruptors, which include bisphenol A, phthalates,
410 pesticides, polychlorinated biphenyls, polybrominated diethyl ethers and dioxins.³⁵ Of
411 particular concern is the high levels of phthalate metabolites that contaminate food and water
412 globally. In keeping with their role in modulating estrogen levels, different phthalate
413 compounds can increase or reduce gestational length and are therefore associated with both
414 pre- and post-term birth.¹⁴³ Governments have sought to ban the use of phthalates in plastics
415 production, however the toxicity of potential replacements is uncertain.³⁵

416

417 **What can be done? The foreground and the horizon**

418 Knowledge of the mechanisms that lead to the birth of a small vulnerable newborn continues
419 to grow as well as our understanding of how to intervene to reduce or prevent this outcome.
420 In the short term, increasing the quantity and quality of antenatal contacts with healthcare

421 providers affords the opportunity to monitor and support physical (weight gain, fetal growth,
422 prevention and treatment of pregnancy complications) and psychological (mental health,
423 agency) wellbeing. Reductions in preterm birth and growth restriction can be achieved with
424 broader implementation of proven antenatal interventions, including multiple micronutrient
425 supplements, balanced protein energy supplements, aspirin, treatment of syphilis, education
426 for smoking cessation, prevention of malaria in pregnancy, treatment of asymptomatic
427 bacteriuria, and progesterone provided vaginally as presented with this series.¹⁴⁴ In addition,
428 the specific vulnerability of those *in utero* to poor air quality, heat waves and toxins in food
429 and water should contribute the urgency of global efforts to reduce harmful environmental
430 exposures and the impact of climate change.

431

432 In the longer term, new knowledge can be used to improve our understanding of the
433 molecular and cellular biology underlying risk factors that inform interventions for
434 populations with the greatest ability to benefit. Risk stratification tools and algorithms that
435 incorporate individual risk profiles, together with biomarkers, can identify individuals who
436 might benefit from pre-emptive care and early pathway-specific interventions. For example, a
437 test that predicts future cervical shortening would identify women who are most likely to
438 benefit from progesterone supplementation without the need for serial ultrasound monitoring.
439 Progesterone supplementation itself is also evolving with new analogues that are resistant to
440 inhibition by the mechanisms that lead to labour.¹⁴⁵ Tests that can be performed and
441 interpreted in the timescale of an antenatal care visit (point-of-care tests) will improve uptake
442 of treatment for infections; treatment can be issued on the same day removing the need to
443 return to clinic for follow-up. Point-of-care tests should fulfil the WHO ASSURED
444 (Affordable, Sensitive, Specific, User-friendly, Rapid, and Equipment-free, and Deliverable)
445 criteria for use in low resource settings.¹⁴⁶

446

447 Placental histopathology is underutilized as a means to diagnose chorioamnionitis and other
448 placental conditions leading to birth of small vulnerable newborns. In cases of preterm pre-
449 labour rupture of membranes, the rupture site is the “scene of the crime” and should be fully
450 investigated. If *Ureaplasma* species are the leading cause of spontaneous preterm birth,
451 prevalence and virulence factors need to be resolved at the level of species. It will be
452 important to demonstrate a causal relationship between species and spontaneous labour and
453 membrane rupture so that antibiotics that can “cure” the individual and prevent these
454 outcomes are not overused.

455

456 There are also new opportunities to understand placental health *in situ*. A particularly
457 promising development is the discovery of extracellular vesicles which are small particles
458 consisting of a lipid bilayer containing the proteins, metabolites, RNA, and DNA that have
459 budded off from a parent cell. In pregnancy, extracellular vesicles in the maternal circulation
460 mainly come from fetal trophoblasts of the placenta.¹⁴⁷ Extracellular vesicles in a peripheral
461 blood may reveal key aspects of the placental environment including oxygen tension, glucose
462 concentration, inflammation, and vascular dysfunction. In abnormal states such as gestational
463 diabetes and pre-eclampsia, numbers of extracellular vesicles are elevated and contain
464 molecular signatures of these conditions.¹⁴⁸

465

466 Every woman’s journey through pregnancy and childbirth is unique and the ultimate goal
467 should be individually tailored care for all with an eye towards optimizing both mother and
468 infant health and wellbeing. Personalized antenatal care does not need to be complex or
469 expensive but the barriers may be higher in low- and middle income settings in comparison
470 with a pragmatic public health approach. Interventions can span from the bedside (e.g., better

471 gestational age assessment) to the clinic (e.g. pre-eclampsia screening) to the operating room
472 (e.g. safer anaesthesia for Caesarean sections) and to society generally (e.g. limiting tobacco
473 or pollution exposure). A more precise deployment of the existing toolkit of interventions is
474 likely to be more cost effective. However, many aspects of even healthy pregnancy remain
475 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%. ⁷¹
Lungs	Ventilation (volume/minute) increases by 50%. ⁷²
Vasculature	Vascular resistance decreases by 30 – 50%. ⁷¹
Red blood cells	Early 10% decrease in RBC and hemoglobin per volume due to increase in plasma volume. ⁷³
White blood cells	Circulating neutrophil counts increase by 50%. ⁷⁴ T cells become less responsive to antigenic stimulation. ⁷⁵
Gastro-intestinal tract	Transit time slows down, possibly to allow longer time for absorption of nutrients. ⁷⁶
Pancreas	Small increase in insulin production in response to mild insulin resistance in maternal tissues. ⁴⁸

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. ⁸¹	Growth restriction
Body composition (underweight, overweight); gestational weight gain (GWG)	Underweight or low GWG: low energy supply. ⁸¹ Overweight or excess GWG: metabolic and hormonal dysregulation, gestational diabetes, hypertension, inflammation. ⁸²	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. ⁸³	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. ⁸⁴	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 F2 α from arachidonic acid. ⁶⁷	Preterm birth

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

Undernutrition	Infection	Characteristics of woman and pregnancy	Environmental exposures and psychosocial stress
Anaemia ²	HIV ⁸	First pregnancy ¹⁷	Unwanted pregnancy ²⁷
Zinc deficiency ³	Malaria ⁹	Adolescent pregnancy ¹⁷	Intimate partner abuse ²⁸
Calcium deficiency ⁴	Syphilis ¹⁰	Short interpregnancy interval ¹⁸	Lack of support or agency ²⁹
Short stature ⁵	Chlamydia ¹¹	Extreme parity ¹⁷	Mental illness ³⁰
Low BMI ⁶	Gonorrhoea ¹²	Older age ¹⁷	Smoking ³¹
Inadequate weight gain ⁷	Urinary tract infection ¹³	Preeclampsia ¹⁹	Alcohol abuse ³²
	Bacterial vaginosis ¹⁴	Placental dysfunction ²⁰	Drug abuse ³³
	Trichomonas vaginalis ¹⁵	Gestational diabetes ²¹	Toxins ³⁴
	Group B Streptococcus ¹⁶	Hypothyroidism ²²	Endocrine disruptors ³⁵
		Cervical weakness ²³	Indoor air pollution ³⁶
		Uterine malformations ²⁴	Outdoor air pollution ³⁷
		Endometriosis ²⁵	Heat waves ³⁸
		Multiple pregnancy ²⁶	High altitude ³⁹

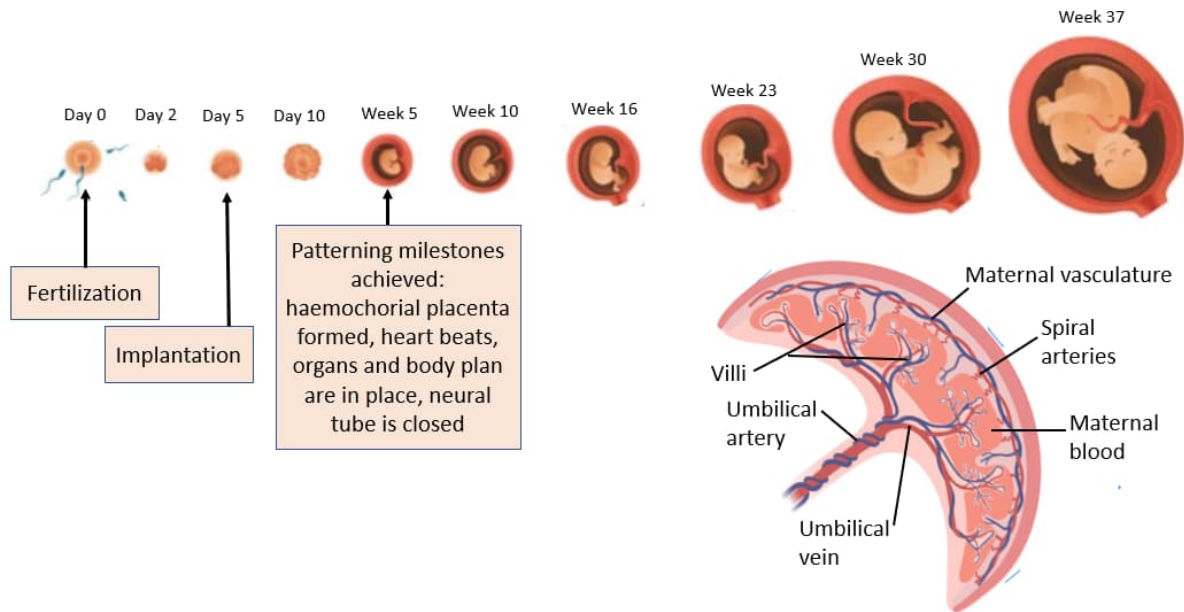


Figure 1. Developing fetus and fully developed placenta. The basic body plan with rudimentary organs are in place by 5 weeks post fertilization. The umbilical artery carries deoxygenated, waste-replete, nutrient-depleted fetal blood to the placental villi where waste is exchanged for nutrients and carbon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

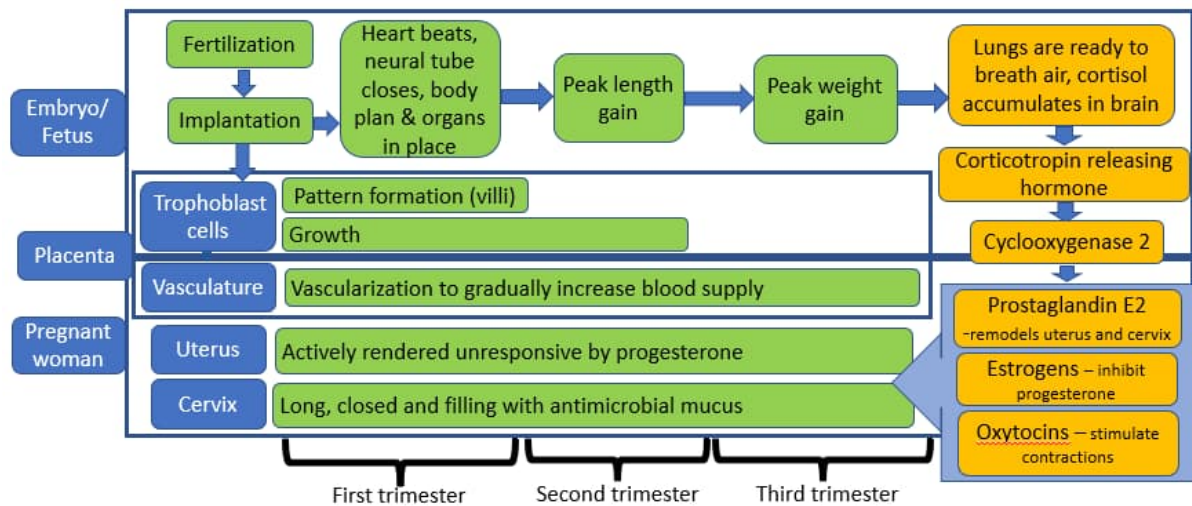


Figure 2. Conceptual model of key determinants of gestational length. When the fetus is ready to be born, cortisol enters the placenta and circulation and activates cyclooxygenase-2 to generate prostaglandin E2, which directs cervical and uterine remodelling. Estrogens override the suppressive effects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

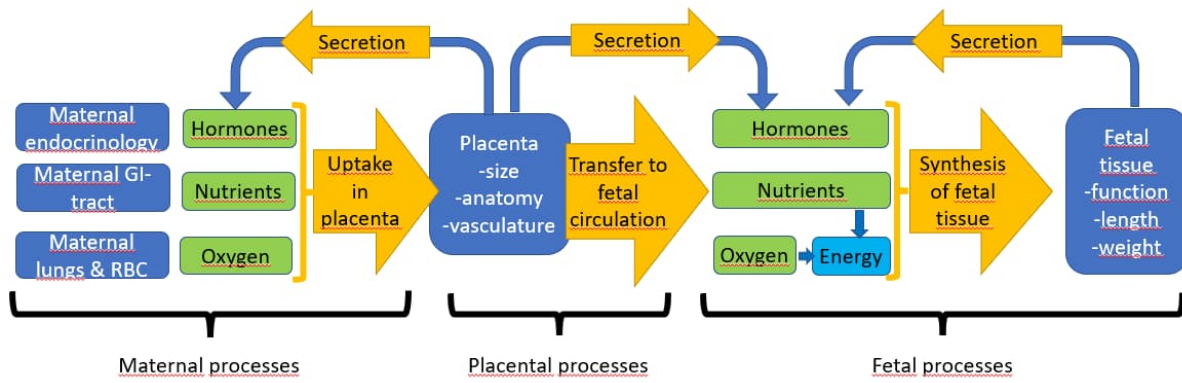
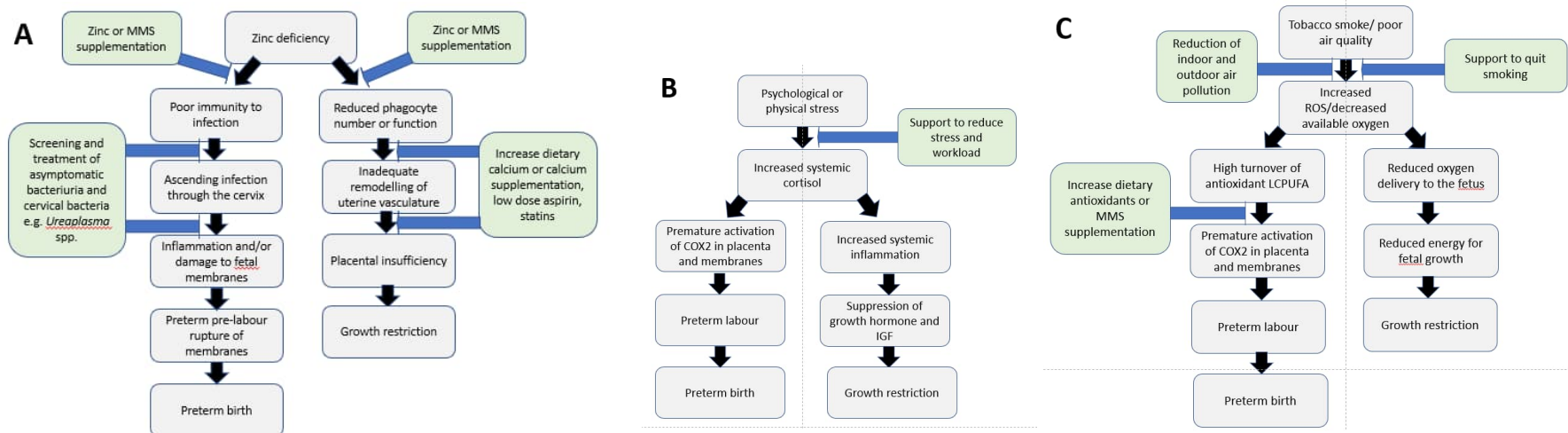


Figure 3. Conceptual model of key determinants of fetal growth. Hormones, nutrients and oxygen from the mother are taken up by the placenta and transferred to the fetal circulation to support synthesis of fetal tissue.

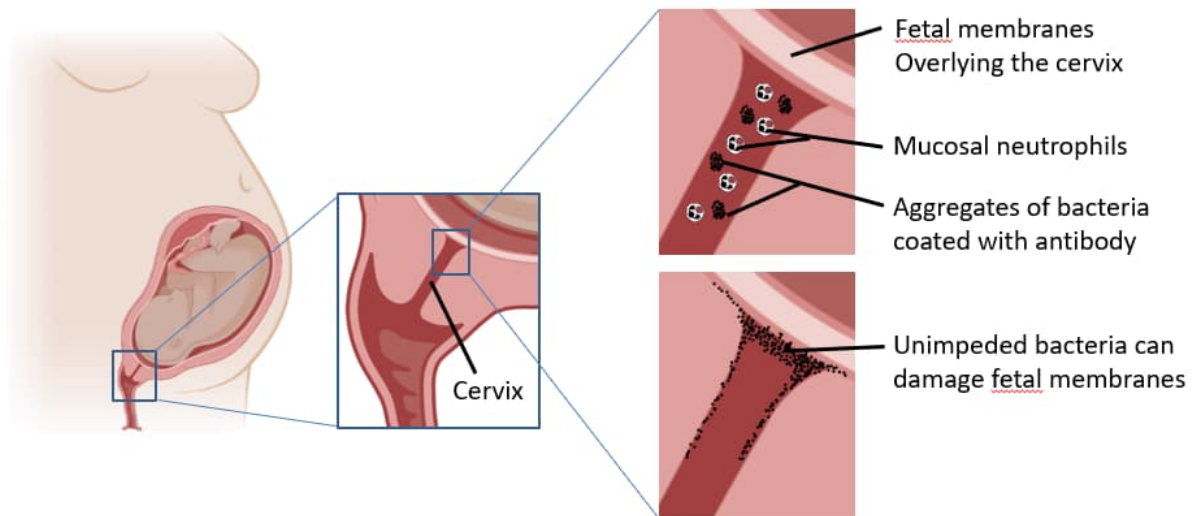


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3 Figure 4. Examples of exposures that are able to contribute to both preterm birth and growth restriction via different pathways and ways to
 4 intervene toward prevention. Zinc deficiency (A), psychological and physical stress (B) and poor air quality/tobacco 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.

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

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