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Barriers to progress in pregnancy research: how can we break through?

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Abstract

Healthy pregnancies are fundamental to healthy populations, but very few therapies to improve pregnancy outcomes are available. Fundamental concepts, for example, placentation or the mechanisms controlling the onset of labor, remain understudied and incompletely understood. A key issue is that research efforts must capture the complexity of the tripartite maternal-placental-fetal system, the dynamics of which change throughout gestation. Studying pregnancy disorders is complicated by the difficulty of creating maternal-fetal-placental interfaces in vitro and the uncertain relevance of animal models to human pregnancy. However, newer approaches include trophoblast organoids to model the developing placenta and integrated data-science approaches to study longer-term outcomes. These approaches provide insights into the physiology of healthy pregnancy, the first step to identifying therapeutic targets in pregnancy disorders.

Main text

Introduction

Pregnancy health is a key determinant of population health, with around 85% of women experiencing pregnancy during their lifetime (*1*). Pregnancy and childbirth have profound effects on immediate and life-course health for both infants and mothers. It is therefore crucial to develop effective methods for preventing and treating pregnancy complications. Pregnancy complications are common (Table 1) and increasing, as more women globally enter pregnancy with comorbidities, including obesity, advanced age, and coexisting medical disorders (*2*). At present there are very few therapies designed specifically for pregnancy conditions, and there has been a virtual absence of new products coming to market in recent years (*3*, *4*). Excluding reformulations, in the last 30 years there have been two drugs licensed for use in pregnancy. Atosiban is an oxytocin antagonist licensed as a preterm labor treatment in the UK but not the USA. Makena (hydroxyprogesterone caproate injection) was approved for use in pregnancy for preterm birth prevention in the USA, but approval has now been revoked (*5*). Another two drugs (carboprost, a synthetic prostaglandin; and carbetocin, an oxytocin agonist) have been licensed for postpartum use for bleeding control. The reasons for lack of progress to safe and effective treatments for pregnancy complications are complex. It seems likely that systemic sexism and paternalism contribute, coupled with risk averse or defensive practices leading to purposive exclusion of pregnant women from research (*6*). Pregnancy is also particularly challenging to study. Firstly, pregnancy complications result from three-way interactions between the pregnant woman, the developing baby, and the placenta, which are complex to model *in vitro*. Secondly, evolving changes over gestation need to be accounted for. Thirdly, *in vivo* study of human pregnancy is restricted by the inaccessibility of samples from within the uterine environment. Finally, striking disparities in pregnancy outcomes exist between and within countries. This indicates

that interactions between social determinants of health and biological pathways must be considered if progress is going to be made on a global scale.

We explore three examples of fundamental knowledge gaps, each of which is often considered to relate to one particular aspect of the maternal-placental-fetal triad: placenta (pre-eclampsia), mother (gestational diabetes), and fetus (preterm birth). We aim to illustrate how each is more usefully considered in the context of a dynamic tripartite system, and highlight promising research directions.

Pre-eclampsia

The placenta is a pregnancy-specific organ that grows *de novo* from the extraembryonic tissues of the conceptus, interfacing with both the maternal and the fetal circulations to sustain fetal development. The placenta dynamically adopts the functions of lungs, kidney, gut, endocrine, and many other body systems to maintain fetal homeostasis throughout pregnancy. Placental support for the fetus also extends to subverting maternal physiology, for example altering cardiac output to meet fetal requirements (*7*) However, complete dependence on the placenta as a flexible support system also carries risk to the fetus. Placentas are unlike other human organs in that they grow rapidly - from a few cells to full-size in a few short weeks - but they also age rapidly (*8*). Tiny variations in placental development at the start of pregnancy can lead to catastrophic failure to sustain later fetal growth. In the earliest stages of pregnancy, optimal establishment of placentation, particularly interaction with maternal decidual cells (*9*), is crucial to reduce the risk of life-threatening disorders such as pre-eclampsia.

Pre-eclampsia affects 2-8% of all pregnancies worldwide (*10*) and remains a major cause of maternal and fetal mortality. Pre-eclampsia (at least in its early-onset form) results from incomplete conversion of the uterine spiral arteries by a particular subset of placental cells, the extravillous trophoblast, in a process that is fundamental to healthy pregnancy, yet incompletely understood (Figure 1). The quality of the interaction between the trophoblast

and the maternal decidua depends on a complex multitude of factors, including both maternal and paternal genetics (*11*). Sub-optimal connections between the developing placenta and the uterus early in pregnancy result in a constellation of damaging sequelae as pregnancy progresses, including severe maternal hypertension and fetal growth restriction (*12*).

Despite the high global burden of morbidity associated with pre-eclampsia (*10*), current strategies for treatment remain crude and poorly-targeted. Magnesium sulphate and antihypertensives are the mainstays of therapy. Maintaining control of maternal blood pressure is essential, but the antihypertensives used to treat pre-eclampsia are limited and old-fashioned. Labetalol, a combined alpha and beta blocker, is commonly used. Labetalol is relatively inefficient at reducing blood pressure and, despite decades of use, its pharmacokinetics in pregnancy remain poorly understood (*13*). Importantly, no drug currently used in the treatment of pre-eclampsia modifies the underlying disease process, which is the culmination of events that begin months earlier during early placentation. There is an urgent need to understand more about these early stages of placental development with a view to identifying targets for the prevention of pre-eclampsia and treatment of severe early-onset pre-eclampsia.

For pre-eclampsia prevention, repurposed basic drugs are in current clinical use including calcium and low-dose aspirin (<300 mg) (*14*). Although evidence from clinical trials suggests that aspirin is effective in reducing the risk of pre-eclampsia by ~60% in selected women, whose risk of preterm pre-eclampsia was >1:100 using a biomarker and risk-factor based screening algorithm (*15*), there is no clarity on the underlying mechanism of action. Possible theories include a direct effect on the extravillous trophoblast cells, reduction of platelet aggregation reducing the risk of placental infarction, or reduction of endothelial activation in the maternal circulation (reviewed in (*16*)). Our inability to distinguish between these theories exemplifies the difficulties with placental drug targeting.

Human placentas have several unique features, meaning that results from animal models are less directly applicable than in other areas of medicine. There is an enormous amount of variability among eutherian mammals in the basic structure and function of the placenta, reflecting both placental evolution and the ecological niche of various species (*17*). For experiments studying many functions, for example oxygen or glucose transport, mammals such as sheep are extremely useful, but crucially only other great apes share human patterns of placental invasion in early pregnancy. In humans the extravillous trophoblast invades both through the uterus towards the maternal vessels and down the lumen of the uterine spiral arteries (Figure 1). Given the importance of trophoblast invasion as the initiating event for pre-eclampsia, results from models in which this does not occur are less readily translatable.

A recent advance that is likely to prove important insights into fundamental placental biology is the development of placental organoids. These differentiate *in vitro* into both the cellular and syncytial components of placental epithelial cells within matrigel droplets (*18*). In the context of pre-eclampsia research, they can be induced to differentiate into extravillous trophoblast. Having a stable, renewable, 3D 'placenta-in-a-dish' containing multiple fully differentiated epithelial lineages opens possibilities for discovery of targeted therapeutics. Current limitations include the 'inside-outside' structure of the organoids (Figure 2), although whether there are any functional implications of this structure is presently unclear. Alternative methods for investigating the biology of early trophoblast include cultured trophoblast stem cells (*19, 20*), which are easier to culture in large numbers, but lack 3D structure and cell interaction. A further approach, which avoids the use of immortalized cell lines, is to derive fresh syncytiotrophoblast cultures (*21*), however this negates the advantages of studying the interplay between different trophoblast lineages.

Future horizons in this work include moving towards developing stable co-culture systems to model the maternal-placental-fetal triad. It is also now possible to derive organoids recapitulating single decidual cells from maternal uterine tissue, opening up possibilities for

combined model systems that include both trophoblast and decidual components (*22*). Pre-eclampsia is a disorder arising from the quality of the interaction between the mother and the placenta, and therefore finding potential therapeutic targets relies on being able to study trophoblast behaving as it would in healthy human pregnancy.

Gestational diabetes

Integrating maternal aspects with fetal and placental model systems is also necessary to advance research into disorders that arise from maternal adaptation to pregnancy. Pregnancy involves subversion of normal maternal homeostatic control for fetal benefit, encompassing virtually every physiological system. These changes are largely driven by placental hormone production, which changes over the course of pregnancy to reflect fetal requirements. While these demands remain within the boundaries of physiological reserve in otherwise healthy mothers, underlying maternal disease tendencies are revealed when this capacity is exceeded. With global shifts in maternity populations towards later age at first birth and high rates of maternal obesity, the risk of pregnancy unmasking underlying physiological vulnerabilities increases. Compromised maternal adaptation to pregnancy carries serious consequences for the survival of both mother and baby.

A key example of maladaptation of maternal physiology is gestational diabetes. Pregnant women develop relative insulin resistance, driven by placental hormone synthesis (*23*), to ensure more circulating glucose is available for fetal growth. Gestational diabetes arises when normal circulating glucose thresholds are exceeded (Figure 3). In addition to unmasking an elevated lifetime risk of type 2 diabetes in the mother, gestational diabetes carries risks for the fetus; fetal overgrowth and neonatal complications are problematic in the short-term (*24*), in addition to longer-term metabolic dysregulation into childhood (*25*). With ~1 in 6 pregnancies globally affected by gestational diabetes (*26*), this is a problem that threatens population health. Defining optimal treatment strategies for gestational diabetes is thus a high priority for population health.

Currently, treatments used for gestational diabetes are re-purposed directly from those used in type II diabetes; no gestational diabetes-specific therapies are available. Diet and lifestyle modification are first-line therapy, but are only effective in ~50-66% of cases (*27*). Pharmacological options currently recommended in various international guidelines include insulin, glyburide, and metformin, all of which are effective in controlling maternal hyperglycaemia (*28*), however repurposing drugs from standard diabetes care to pregnancy involves consideration of the potential impacts on all aspects of the maternal-placental-fetal triad. The placenta is a key consideration here; while assessing placental transfer of drugs between the maternal and fetal circulations is routine, the direct impact of drugs on the placenta itself is more often overlooked in assessing new therapies. An example is the impact of metformin, a known inhibitor of complex I of the electron transport chain, which reduces placental ATP production (*21*) and is associated with lower birthweight (*28*). These findings have led to considerable divergence in opinion regarding metformin as a first-line drug therapy in pregnancy. The example highlights not only the need for more rigorous evaluation of placental impacts of drug therapies in pregnancy, but also the challenge of evaluating the longer-term impacts of intrauterine exposure to therapeutics on health into childhood or beyond. Follow-up of birth cohorts is expensive, slow, and difficult to achieve without introducing marked attrition bias. Studies linking electronic health records and other routinely collected data sources, especially those with enhanced methodologies such as sibling-pairing, will be increasingly important to ensure that subtle alterations in long-term health outcomes arising from suboptimal early life environments can be detected and monitored.

Spontaneous preterm labor

A further critical knowledge gap surrounds the mechanisms controlling the onset of human labor, which must be appropriately timed for optimal birth outcomes. Preterm birth (<37 weeks gestation) affects ~1 in 10 pregnancies, resulting in sequelae ranging from neonatal

death to impaired physical and neurodevelopment (*29*). In contrast, if birth is not achieved by 40 weeks, the risk of stillbirth increases (*30*).

Spontaneous labor at term is a coordinated process involving maternal (cervix, myometrium, decidua) and placental (placenta, and fetal membranes [chorion and amnion]) tissues, accompanied by fetal maturation (*17*). Inflammation is a key feature, but the fundamental mechanisms that control the onset of parturition in humans remain unknown (*17*). In most mammals other than primates, labor is initiated by withdrawal of progesterone (*31*). In human pregnancy there is no drop in circulating progesterone, but there is thought to be locally regulated "functional" progesterone withdrawal (*31*). However, the specific control mechanisms and transcriptional effects of this are not known, highlighting a key problem of using animal models for developing treatments for pregnancy conditions.

During gestation, exogenous stimuli, such as infection or trauma, or endogenous stimuli (including placental insufficiency, hemorrhage, hypoxia, or uterine overdistension), can prematurely stimulate inflammation in various reproductive tract tissues, propagating spontaneous preterm labor (*32*). To date, many studies of preterm labor have focused on the responses of one tissue type. Recently systems biology approaches applied to multiple tissues in tandem have shown promise (*33*). However, technological challenges remain to enable a whole system approach capturing dynamic changes in the maternal, fetal and placental compartments across gestation. This has contributed to a failure to convert promising preclinical targets to effective clinical treatments (*33*).

Currently there are very few effective drugs for the prevention of preterm labor. Progesterone supplementation can sometimes extend gestation in women who are thought to be at high risk of preterm birth. However, injectable 17-alpha-hydroxyprogesterone caproate (Makena) has had US Food and Drug Administration (FDA) approval withdrawn as post market studies failed to confirm clinical benefit (*5*). Vaginal progesterone is widely recommended and used off label for preterm birth prevention instead. However, this also

lacks FDA approval, and there is conflicting evidence as to its efficacy (*34*). Given already high concentrations of circulating progesterone, the mode of action of additional supplementary progesterone is not known.

An alternative widely-used preventive treatment in women with an increased risk of preterm birth is cervical cerclage. This is where a mesh or monofilament suture is inserted through the body of the cervix to help keep it closed, carries risk of complications including damage to the cervix, bleeding, and membrane rupture (*35*). A problem with both progesterone and cervical cerclage is the identification of individuals who most benefit from treatment. At present, the risk of preterm birth is usually based on non-specific clinical features such as a history of preterm birth, or emerging signs of preterm labor such as a short cervix on ultrasound. Efforts to better understand both the genotype and phenotype of preterm birth, which has multiple underlying etiologies, may help to determine groups that benefit from these treatments, as well as identifying much needed new treatment targets.

In women with signs and symptoms of spontaneous preterm labor, tocolytic agents may temporarily slow or stop contractions, buying time to administer corticosteroids to promote fetal maturation or to access a higher-level healthcare facility. Recommended agents vary by country, but include calcium channel blockers, betamimetics, nitric oxide donors, cyclooxygenase inhibitors, magnesium sulphate, and oxytocin receptor antagonists. In general, there is evidence that they may prolong pregnancy for 2 days to one week, but they have maternal side effects and evidence of neonatal or longer term benefit is absent (*36*).

Much of the effort to develop preterm birth treatments focuses on identifying candidates which prolong gestation (*37*). This assumes that advancing gestation will benefit infant outcomes, given that the severity of preterm morbidity is inversely related to gestation at birth. However, preterm labor is the final common pathway of multiple intrauterine challenges that can threaten the developing fetus (*32*). Infection, placental insufficiency, hemorrhage, and hypoxia are examples of direct risks to fetal life that are resolved by spontaneous or

iatrogenic preterm birth. Injudicious treatments to keep a baby in a toxic uterine environment may thus be damaging, with potential long-lasting effects on childhood development. To optimize infant outcomes, we need to move to an approach which includes: i) early identification and treatment of pathologies that can lead to preterm labor, ii) individualized evaluation of both the fetal and maternal responses to such threats, and iii) timed birth when the risks of continuing pregnancy outweigh the risks of prematurity. Focusing only on modulating the onset, or progress, of preterm labor, as most trials to date have done (*38*), only addresses the last part of this paradigm. In parallel, we need better methods of assessing fetal wellbeing and effects on development, with therapeutics aimed at modifying underlying causes. The coordinated application of advances in *in utero* imaging (*39*), development of wearable monitors (*40*), and identification of circulating biomarkers such as nucleic acids (*41*), is a promising strategy towards this goal.

Conclusion

Development of therapies to treat pregnancy-related conditions is currently inadequate. For all of the conditions we discuss, progress towards new therapies would be enhanced by the identification of improved biomarkers to stratify risk and target therapeutics. Currently, the biomarkers in clinical use either have poor predictive power (SFlt/PlGF in pre-eclampsia) or are the manifestations of the conditions themselves (blood glucose in GDM and fetal fibronectin in preterm birth). Sequencing of extracellular RNA circulating in maternal blood is an exciting new development with potential for prediction of pregnancy complications (*41*).

In the absence of safe and effective treatments, large numbers of women and their babies will continue to get sick or die. More research that takes an integrated approach to the dynamic interactions of the maternal-placental-fetal triad is urgently required. This may involve looking outside the traditional methodologies of laboratory animal and observational human cohort studies used in pregnancy research, towards techniques used in other disciplines, for example development of digital twins and 3D tissue architecture models.

Addressing major gaps in our fundamental understanding of the physiology of pregnancy, development, and birth is necessary to identify candidate therapeutic targets for the benefit of future population health.

References and notes

1. T. Valerio, B. Knop, R. M. Kreider, W. He, "Childless Older Americans: 2018" in *Current Population Reports*, U.S. Census Bureau, Ed. (U.S. Government Printing Office, Washington, DC, , 2021), pp. 70–173.

2. C. C. Brown, C. E. Adams, K. E. George, J. E. Moore, Associations Between Comorbidities and Severe Maternal Morbidity. *Obstet. Gynecol.* **136**, 892–901 (2020).

3. N. M. Fisk, R. Atun, Market failure and the poverty of new drugs in maternal health. *PLoS Med.* **5**, e22 (2008).

4. L. C. Chappell, A. L. David, Improving the Pipeline for Developing and Testing Pharmacological Treatments in Pregnancy. *PLoS Med.* **13**, e1002161 (2016).

5. D. G. Aaron, I. G. Cohen, E. Y. Adashi, The FDA Struggle to Withdraw Makena: Problems With the Accelerated Approval Process. *JAMA*. **328**, 2394–2395 (2022).

6. S. J. Stock, J. E. Norman, Medicines in pregnancy. *F1000Res.* **8** (2019), doi:10.12688/f1000research.17535.1.

7. K. P. Conrad, S. Taher, Y.-Y. Chi, Y. Qiu, M. Li, M. Lingis, R. S. Williams, A. Rhoton-Vlasak, M. Keller-Wood, M. S. Segal, Relationships between reproductive hormones and maternal pregnancy physiology in women conceiving with or without in vitro fertilization. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **321**, R454–R468 (2021).

8. K. Maiti, Z. Sultana, R. J. Aitken, J. Morris, F. Park, B. Andrew, S. C. Riley, R. Smith, Evidence that fetal death is associated with placental aging. *Am. J. Obstet. Gynecol.* **217**, 441.e1–441.e14 (2017).

9. O. Huhn, M. A. Ivarsson, L. Gardner, M. Hollinshead, J. C. Stinchcombe, P. Chen, N. Shreeve, O. Chazara, L. E. Farrell, J. Theorell, H. Ghadially, P. Parham, G. Griffiths, A. Horowitz, A. Moffett, A. M. Sharkey, F. Colucci, Distinctive phenotypes and functions of innate lymphoid cells in human decidua during early pregnancy. *Nat. Commun.* **11**, 381 (2020).

10. E. Abalos, C. Cuesta, G. Carroli, Z. Qureshi, M. Widmer, J. P. Vogel, J. P. Souza, WHO Multicountry Survey on Maternal and Newborn Health Research Network, Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG*. **121 Suppl 1**, 14–24 (2014).

11. S. E. Hiby, J. J. Walker, K. M. O'shaughnessy, C. W. G. Redman, M. Carrington, J. Trowsdale, A. Moffett, Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success. *J. Exp. Med.* **200**, 957–965 (2004).

12. P. Von Dadelszen, A. Syngelaki, R. Akolekar, L. A. Magee, K. H. Nicolaides, Preterm and term pre-eclampsia: relative burdens of maternal and perinatal complications.

BJOG (2022), doi:10.1111/1471-0528.17370.

13. D. van de Vusse, P. Mian, S. Schoenmakers, R. B. Flint, W. Visser, K. Allegaert, J. Versmissen, Pharmacokinetics of the most commonly used antihypertensive drugs throughout pregnancy methyldopa, labetalol, and nifedipine: a systematic review. *Eur. J. Clin. Pharmacol.* **78**, 1763–1776 (2022).

14. T. Liabsuetrakul, Y. Yamamoto, C. Kongkamol, E. Ota, R. Mori, H. Noma, Medications for preventing hypertensive disorders in high-risk pregnant women: a systematic review and network meta-analysis. *Syst. Rev.* **11**, 135 (2022).

15. D. L. Rolnik, D. Wright, L. C. Poon, N. O'Gorman, A. Syngelaki, C. de Paco Matallana, R. Akolekar, S. Cicero, D. Janga, M. Singh, F. S. Molina, N. Persico, J. C. Jani, W. Plasencia, G. Papaioannou, K. Tenenbaum-Gavish, H. Meiri, S. Gizurarson, K. Maclagan, K. H. Nicolaides, Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *N. Engl. J. Med.* **377**, 613–622 (2017).

16. S. W. Walsh, J. F. Strauss 3rd, The Road to Low-Dose Aspirin Therapy for the Prevention of Preeclampsia Began with the Placenta. *Int. J. Mol. Sci.* **22** (2021), doi:10.3390/ijms22136985.

17. R. Smith, Parturition. *N. Engl. J. Med.* **356**, 271–283 (2007).

18. M. Y. Turco, L. Gardner, R. G. Kay, R. S. Hamilton, M. Prater, M. S. Hollinshead, A. McWhinnie, L. Esposito, R. Fernando, H. Skelton, F. Reimann, F. M. Gribble, A. Sharkey, S. G. E. Marsh, S. O'Rahilly, M. Hemberger, G. J. Burton, A. Moffett, Trophoblast organoids as a model for maternal-fetal interactions during human placentation. *Nature*. **564**, 263–267 (2018).

19. H. Okae, H. Toh, T. Sato, H. Hiura, S. Takahashi, K. Shirane, Y. Kabayama, M. Suyama, H. Sasaki, T. Arima, Derivation of Human Trophoblast Stem Cells. *Cell Stem Cell*. **22**, 50–63.e6 (2018).

20. C. Dong, T. W. Theunissen, Generating Trophoblast Stem Cells from Human Naïve Pluripotent Stem Cells. *Methods Mol. Biol.* **2416**, 91–104 (2022).

21. J. L. Tarry-Adkins, I. G. Robinson, R. M. Reynolds, I. L. M. H. Aye, D. S. Charnock-Jones, B. Jenkins, A. Koulmann, S. E. Ozanne, C. E. Aiken, Impact of Metformin Treatment on Human Placental Energy Production and Oxidative Stress. *Front Cell Dev Biol*. **10**, 935403 (2022).

22. M. Y. Turco, L. Gardner, J. Hughes, T. Cindrova-Davies, M. J. Gomez, L. Farrell, M. Hollinshead, S. G. E. Marsh, J. J. Brosens, H. O. Critchley, B. D. Simons, M. Hemberger, B.-K. Koo, A. Moffett, G. J. Burton, Long-term, hormone-responsive organoid cultures of human endometrium in a chemically defined medium. *Nat. Cell Biol.* **19**, 568–577 (2017).

23. H. D. McIntyre, R. Serek, D. I. Crane, T. Veveris-Lowe, A. Parry, S. Johnson, K. C. Leung, K. K. Ho, M. Bougoussa, G. Hennen, A. Igout, F. Y. Chan, D. Cowley, A. Cotterill, R. Barnard, Placental growth hormone (GH), GH-binding protein, and insulin-like growth factor axis in normal, growth-retarded, and diabetic pregnancies: correlations with fetal growth. *J. Clin. Endocrinol. Metab.* **85**, 1143–1150 (2000).

24. W. Ye, C. Luo, J. Huang, C. Li, Z. Liu, F. Liu, Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ*. **377**, e067946 (2022).

25. W. L. Lowe Jr, L. P. Lowe, A. Kuang, P. M. Catalano, M. Nodzenski, O. Talbot, W.-H. Tam, D. A. Sacks, D. McCance, B. Linder, Y. Lebenthal, J. M. Lawrence, M. Lashley, J. L. Josefson, J. Hamilton, C. Deerochanawong, P. Clayton, W. J. Brickman, A. R. Dyer, D. M. Scholtens, B. E. Metzger, HAPO Follow-up Study Cooperative Research Group, Maternal glucose levels during pregnancy and childhood adiposity in the Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study. *Diabetologia*. **62**, 598–610 (2019).

26. H. Wang, N. Li, T. Chivese, M. Werfalli, H. Sun, L. Yuen, C. A. Hoegfeldt, C. Elise Powe, J. Immanuel, S. Karuranga, H. Divakar, N. Levitt, C. Li, D. Simmons, X. Yang, IDF Diabetes Atlas Committee Hyperglycaemia in Pregnancy Special Interest Group, IDF Diabetes Atlas: Estimation of Global and Regional Gestational Diabetes Mellitus Prevalence for 2021 by International Association of Diabetes in Pregnancy Study Group's Criteria. *Diabetes Res. Clin. Pract.* **183**, 109050 (2022).

27. HAPO Study Cooperative Research Group, B. E. Metzger, L. P. Lowe, A. R. Dyer, E. R. Trimble, U. Chaovarindr, D. R. Coustan, D. R. Hadden, D. R. McCance, M. Hod, H. D. McIntyre, J. J. N. Oats, B. Persson, M. S. Rogers, D. A. Sacks, Hyperglycemia and adverse pregnancy outcomes. *N. Engl. J. Med.* **358**, 1991–2002 (2008).

28. J. L. Tarry-Adkins, C. E. Aiken, S. E. Ozanne, Comparative impact of pharmacological treatments for gestational diabetes on neonatal anthropometry independent of maternal glycaemic control: A systematic review and meta-analysis. *PLoS Med.* **17**, e1003126 (2020).

29. R. L. Goldenberg, J. F. Culhane, J. D. Iams, R. Romero, Epidemiology and causes of preterm birth. *Lancet*. **371**, 75–84 (2008).

30. J. Muglu, H. Rather, D. Arroyo-Manzano, S. Bhattacharya, I. Balchin, A. Khalil, B. Thilaganathan, K. S. Khan, J. Zamora, S. Thangaratinam, Risks of stillbirth and neonatal death with advancing gestation at term: A systematic review and meta-analysis of cohort studies of 15 million pregnancies. *PLoS Med.* **16**, e1002838 (2019).

31. B. F. Mitchell, M. J. Taggart, Are animal models relevant to key aspects of human parturition? *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **297**, R525–45 (2009).

32. R. Romero, S. K. Dey, S. J. Fisher, Preterm labor: one syndrome, many causes. *Science*. **345**, 760–765 (2014).

33. M. S. Vidal Jr, R. C. V. Lintao, M. E. L. Severino, O. A. G. Tantengco, R. Menon, Spontaneous preterm birth: Involvement of multiple feto-maternal tissues and organ systems, differing mechanisms, and pathways. *Front. Endocrinol.* . **13**, 1015622 (2022).

34. EPPPIC Group, Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. *Lancet*. **397**, 1183–1194 (2021).

35. Z. Alfirevic, T. Stampalija, N. Medley, Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. *Cochrane Database Syst. Rev.* **6**, CD008991 (2017).

36. A. Wilson, V. A. Hodgetts-Morton, E. J. Marson, A. D. Markland, E. Larkai, A. Papadopoulou, A. Coomarasamy, A. Tobias, D. Chou, O. T. Oladapo, M. J. Price, K. Morris, I. D. Gallos, Tocolytics for delaying preterm birth: a network meta-analysis (0924). *Cochrane Database Syst. Rev.* (2022), doi:10.1002/14651858.CD014978.pub2.

37. A. R. A. McDougall, A. Tuttle, M. Goldstein, A. Ammerdorffer, L. Aboud, A. M. Gülmezoglu, J. P. Vogel, Expert consensus on novel medicines to prevent preterm birth

and manage preterm labour: Target product profiles. *BJOG* (2022), doi:10.1111/1471-0528.17314.

38. N. Medley, J. P. Vogel, A. Care, Z. Alfirevic, Interventions during pregnancy to prevent preterm birth: an overview of Cochrane systematic reviews. *Cochrane Database Syst. Rev.* **11**, CD012505 (2018).

39. N. Andescavage, C. Limperopoulos, Emerging placental biomarkers of health and disease through advanced magnetic resonance imaging (MRI). *Exp. Neurol.* **347**, 113868 (2022).

40. D. Ryu, D. H. Kim, J. T. Price, J. Y. Lee, H. U. Chung, E. Allen, J. R. Walter, H. Jeong, J. Cao, E. Kulikova, H. Abu-Zayed, R. Lee, K. L. Martell, M. Zhang, B. R. Kampmeier, M. Hill, J. Lee, E. Kim, Y. Park, H. Jang, H. Arafa, C. Liu, M. Chisembele, B. Vwalika, N. Sindano, M. B. Spelke, A. S. Paller, A. Premkumar, W. A. Grobman, J. S. A. Stringer, J. A. Rogers, S. Xu, Comprehensive pregnancy monitoring with a network of wireless, soft, and flexible sensors in high- and low-resource health settings. *Proc. Natl. Acad. Sci. U. S. A.* **118** (2021), doi:10.1073/pnas.2100466118.

41. M. Rasmussen, M. Reddy, R. Nolan, J. Camunas-Soler, A. Khodursky, N. M. Scheller, D. E. Cantonwine, L. Engelbrechtsen, J. D. Mi, A. Dutta, T. Brundage, F. Siddiqui, M. Thao, E. P. S. Gee, J. La, C. Baruch-Gravett, M. K. Santillan, S. Deb, S. M. Ame, S. M. Ali, M. Adkins, M. A. DePristo, M. Lee, E. Namsaraev, D. J. Gybel-Brask, L. Skibsted, J. A. Litch, D. A. Santillan, S. Sazawal, R. M. Tribe, J. M. Roberts, M. Jain, E. Høgdall, C. Holzman, S. R. Quake, M. A. Elovitz, T. F. McElrath, RNA profiles reveal signatures of future health and disease in pregnancy. *Nature*. **601**, 422–427 (2022).

42. S. Chawanpaiboon, J. P. Vogel, A.-B. Moller, P. Lumbiganon, M. Petzold, D. Hogan, S. Landoulsi, N. Jampathong, K. Kongwattanakul, M. Laopaiboon, C. Lewis, S. Rattanakanokchai, D. N. Teng, J. Thinkhamrop, K. Watananirun, J. Zhang, W. Zhou, A. M. Gülmezoglu, Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health*. **7**, e37–e46 (2019).

43. H. Blencowe, J. Krasevec, M. de Onis, R. E. Black, X. An, G. A. Stevens, E. Borghi, C. Hayashi, D. Estevez, L. Cegolon, S. Shiekh, V. Ponce Hardy, J. E. Lawn, S. Cousens, National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health*. **7**, e849–e860 (2019).

44. T. Firoz, C. L. Trigo Romero, C. Leung, J. P. Souza, Ö. Tunçalp, Global and regional estimates of maternal near miss: a systematic review, meta-analysis and experiences with application. *BMJ Glob Health*. **7** (2022), doi:10.1136/bmjgh-2021-007077.

45. G. Carroli, C. Cuesta, E. Abalos, A. M. Gulmezoglu, Epidemiology of postpartum haemorrhage: a systematic review. *Best Pract. Res. Clin. Obstet. Gynaecol.* **22**, 999–1012 (2008).

46. S. L. Woodd, A. Montoya, M. Barreix, L. Pi, C. Calvert, A. M. Rehman, D. Chou, O. M. R. Campbell, Incidence of maternal peripartum infection: A systematic review and meta-analysis. *PLoS Med.* **16**, e1002984 (2019).

47. J. J. Kurinczuk, M. White-Koning, N. Badawi, Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. *Early Hum. Dev.* **86**, 329–338 (2010).

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Tables and Figures

Table 1: Global estimates of the incidence of selected pregnancy complications

Condition	Global estimate	Reference
Preterm birth (before 37 weeks gestation)	10·6% (UI 8.7-11.9)[a]	*(42)*
Pre-eclampsia	2.16% (95% CI 2.11 to 2.22)[b]	(*10*)
Gestational Diabetes	14.0% (95% CI 13.97 to 14.04)[c]	(*26*)
Low birthweight (<2500 gram)	14.6 % (UI 12·4 to 17·1)[a]	(*43*)
Maternal near miss (maternal life-threatening complication)	1.4% (95% CI 0.4 to 2.5)[d]	(*44*)
Postpartum Haemorrhage	6.09% (95% CI 6.06 to 6.11)[e]	(*45*)
Infection		(*46*)
Chorioamnionitis	3.9% (95% CI 1.8-6.8)[e]	(*46*)
Sepsis	0.05% (95% CI 0.03-0.07)[e]	(*46*)

Birth asphyxia (Hypoxic Ischemic Encephalopathy)	0.15% (95 % CI 0.13-0.17[a]	(*47*)

[a] per 100 livebirths; [b] per 100 pregnancies; [c] per 100 pregnancies ≥24 weeks gestation; [d] per 100 deliveries or livebirths; [e] per 100 births. UI: Uncertainty Interval. CI: Confidence interval

High quality data on specific morbidities, and maternal and perinatal deaths are not available in many settings. This is a barrier to pregnancy research. In this table we present best available global estimates.

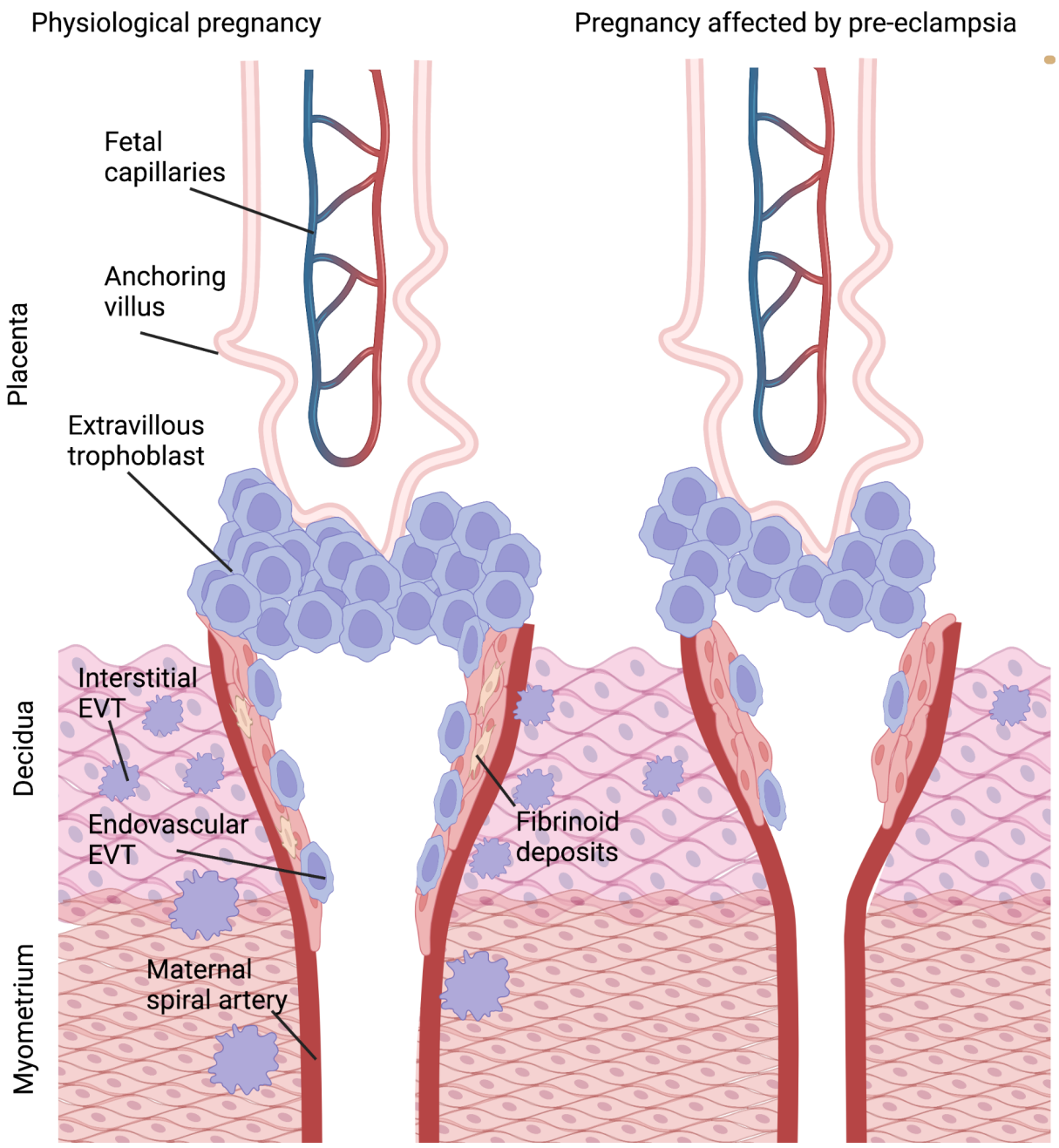

Figure 1: Limited conversion of the spiral arteries in the context of pre-eclampsia

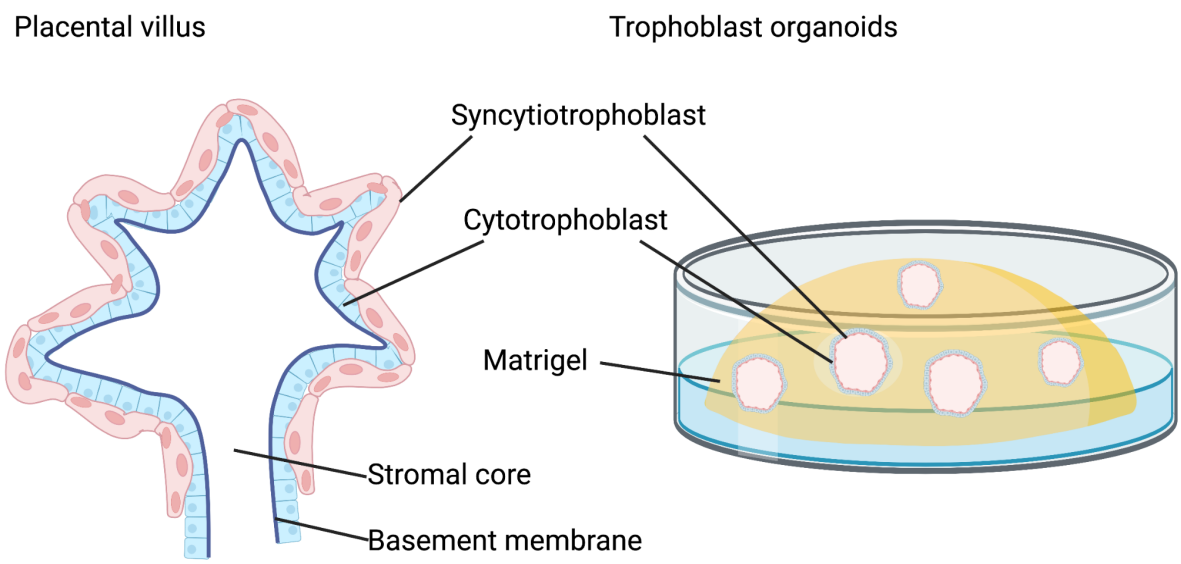

Figure 2: 'Inside-out' structure of trophoblast organoids derived from first-trimester placental villi

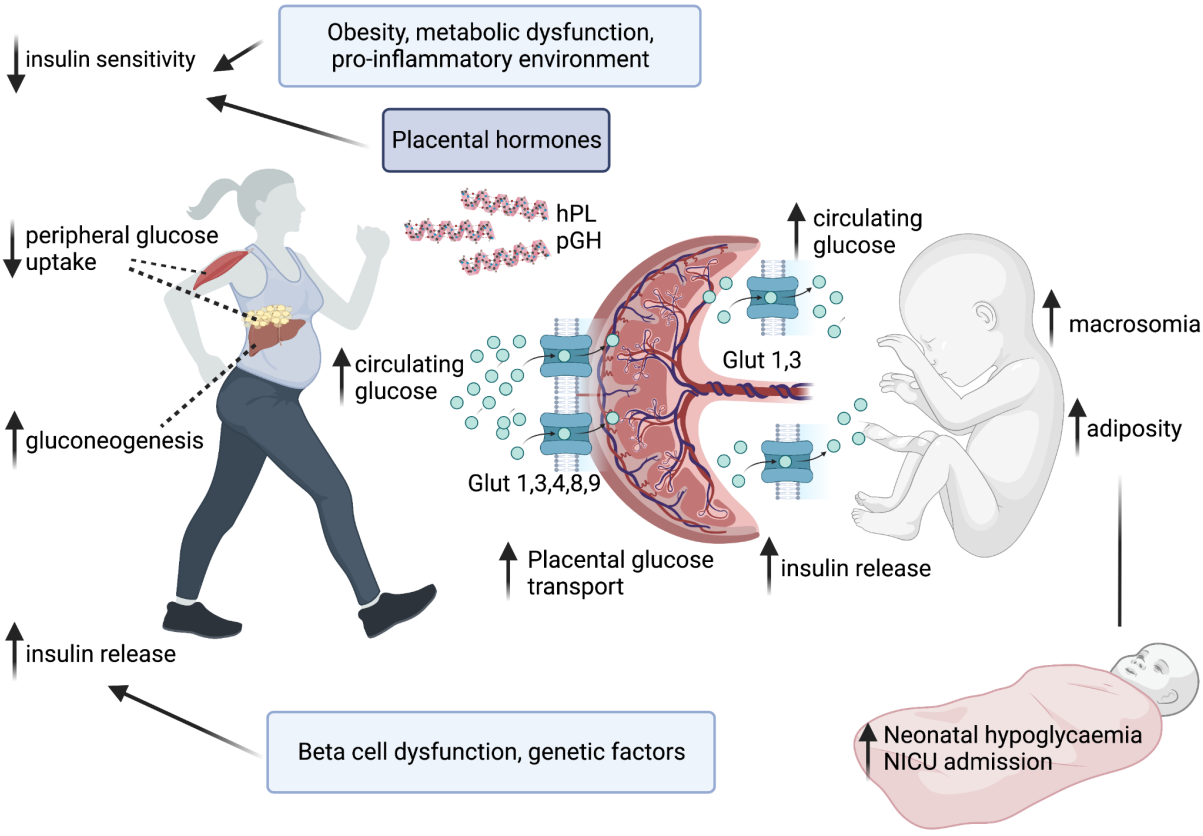

Figure 3: Current understanding of the pathophysiology of gestational diabetes. The addition of placental hormones (hPL; human placental lactogen, pGH; placental growth

hormone) in a mother with one or more risk factors for diabetes (obesity, insulin resistance, other metabolic dysfunction, beta cell dysfunction, genetic risk factors, high pro-inflammatory cytokines) leads to high maternal circulating glucose. There is subsequent increased facilitated diffusion of glucose across the placenta, provoking high fetal and neonatal insulin release.