Immune-metabolic adaptations in pregnancy: A potential stepping-stone to sepsis

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Summary

Physiological shifts during pregnancy predispose women to a higher risk of developing sepsis resulting from a maladapted host-response to infection. Insightful studies have delineated subtle point-changes to the immune system during pregnancy. Here, we present an overlay of these point-changes, asking what changes and when, at a physiological, cellular, and molecular systems-level in the context of sepsis. We identify distinct immune phases in pregnancy delineated by placental hormone-driven changes in homeostasis setpoints of the immune and metabolic systems that subtly mirrors changes observed in sepsis. We propose that pregnancy immune-metabolic setpoint changes impact feedback thresholds that increase risk for a maladapted host-response to infection and thus act as a stepping-stone to sepsis. Defining maternal immune-metabolic setpoint changes is not only vital for tailoring the right diagnostic tools for early management of maternal sepsis but will facilitate an unravelling of the pathophysiological pathways that predispose an individual to sepsis.

Keywords: Pregnancy; Sepsis; Maternal sepsis; Maternity; Homeostasis; Metabolism; Immunity; Setpoint; Set-point change; Hormones; Vaccines

Introduction

Maternal mortality numbers have been declining; however, they remain unacceptably high. Globally pregnancy-related infections leading to sepsis are the third most common direct cause, representing about 11% of maternal deaths.[1] Although lower in the UK, it was found that for every death, fifty women suffer from extreme morbidities.[2] Mortality rates for COVID-19 are fortunately low in pregnancy, however, the pandemic has globally impacted routine maternal care. A WHO study predicted an additional 57,700 maternal deaths in low-middle income countries (LMICs) as a result of the pandemic,[3] many of which will be attributed to sepsis.

While most maternal infection resolve on their own, maternal physiological and immunological adaptations make women more susceptible to developing sepsis which is defined as: An organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or post-partum period.[4] This is based upon the third consensus for sepsis, which defines organ failure clinically as a Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score >2.[5] However, this is not a settled consensus in pregnancy, as this definition cannot be directly applied to the feto-maternal unit, as the fetus or placenta may have an infection leading to organ failure, which is not always reflected in maternal SOFA scores. Delivery of the baby often removes the source of infection, however at the time of diagnosis it is unknown whether the infection of the feto-maternal unit could lead to sepsis in mother or child. As such, a clinical diagnosis of suspected sepsis is often used to trigger early management, such as intravenous antibiotics to prevent sepsis and maintain feto-maternal health. Even using the obstetric early warning system for sepsis,[6] there is a frequent misdiagnosis of sepsis in the maternal population. Either an initial over diagnosis where antibiotics are given without proof of infection or sign of organ failure, or under diagnosis which results in delayed treatments. This is a clinical dilemma considering the rate of inappropriate antibiotic prescriptions in hospitals is estimated at 30–50%[7] and can cause allergic reactions, gastrointestinal disturbances, cardiac arrhythmia, antibiotic resistance, and death. Additionally, viral sepsis is common in pregnancy.[8] Therefore, there is justifiable demand for both feto-maternal specific biomarkers for sepsis and adoption of immunomodulatory drugs, rather than just relying on antibiotics.

Importantly, pregnancy results in an increased disease severity in infection (a maladapted host-response

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characteristic of sepsis) and not necessarily an increased incidence of infection. Underlying the increased risk of feto-maternal sepsis are alterations in maternal physiology. Many systems with interrelated physiological processes such as the immune and metabolic systems are altered in pregnancy resulting in deviations from normative reference levels. Circulating blood volume increases by about 45%, basal heart rate, cardiac output, and respiratory tidal volume increase, as well as nutrient demands of the fetus exerting pressure on maternal metabolism and bioenergetics.[1,9] The first two trimesters of pregnancy have been described as an anabolic state with increased fat deposition and lower blood glucose. In later stages of pregnancy this shifts toward a catabolic state where fat is broken down and blood glucose is elevated. Adaptive changes in the homeostasis of the immune system are also under stringent regulatory control and interconnected with the physiological, metabolic, and endocrine systems – some of these connections were recently reviewed and described as the 'immune clockworks of pregnancy'.[10] Yet, a full mechanistic and functional understanding for feto-maternal health and implications for immune defence remains challenging. While it is known that the higher risk for sepsis is not caused by a higher frequency of infections, it remains unclear what drives an increase in severity outcome from infection. Here, we expose associations between immune alterations in pregnancy and sepsis and propose that the adaptive changes in immune-metabolic homeostasis setpoints during pregnancy (Box 1) provides a stepping-stone to sepsis.

Implantation and placentation initiate immune and metabolic adaptive alterations

Immune cell changes commence at implantation when the blastocyst attaches to and invades the uterine endometrium. The blastocyst produces human chorionic gonadotropin (hCG) that triggers key mediators of pregnancy progression, including migration of regulatory T-lymphocytes (T-regs) to the uterus[11] and essential alterations in maternal lipid and sugar metabolism and mobilization for fetal growth.[12] These changes, along with PD-1 mediated immune checkpoint control,[13] create and maintain fetal immune tolerance.[14] Subsequently, numbers of T-regs are elevated systemically[15] while other T-lymphocytes can be decreased by approximately 10–20% in the first trimester (Table 1).[16–18] Mild damage to the endometrium and noncanonical HLA molecules in implantation primes an inflammatory response partly driven by uterine NK-cells[19] which upregulates cytokines such as interleukin 1 and 6 (IL-6, IL-1), and leukaemia inhibitory factor (LIF), the latter being vital for implantation.[20] IL-6 may also increase maternal plasma complement concentrations, especially the pro-inflammatory anaphylatoxins.[21] In direct response, early embryos counteract this by expressing complement inhibitors and bind to complement regulators, which prevents rejection.[22] After implantation early first trimester is associated with maintained levels of inflammatory cytokines and growth factors such as Granulocyte and Granulocyte-Macrophage Colony Stimulating Factors (G-CSF, GM-CSF).[23] These molecules are thought to drive enhanced levels of innate immune cells such as neutrophils (15–75% increased) and monocytes (≈15% increase) in the first trimester (Table 1).[16,18,23–25] Importantly, G-CSF commits bone marrow precursors to the neutrophil lineage and is produced copiously by decidual tissues.[26] Neutrophils can also be preferentially recruited to placental tissues, where high levels of IL-8 have been identified,[27] purportedly to protect the fetus from pathogens. Such innate-driven inflammation is becoming recognized as a requirement for wound healing processes,[28] thus, this altered systemic environment may enable adequate repair and maintenance of the uterine epithelium post implantation, placentation, and remodelling of the womb.

In terms of homeostasis, immune stimulation needs to be counteracted to avoid inflammatory-mediated fetal abortion. Therefore, the dynamic setpoint change involves an inhibitory axis driven by increased pregnancy hormones, including the anti-inflammatory progesterone and estrogens, which increase over the course of pregnancy, peaking in the third trimester.[29] They are initially produced by the corpus luteum followed by fetal and placental contributions and are vital for a successful pregnancy. Progesterone and estrogens modulate many aspects of maternal physiology including control over metabolism.[9] For instance, both hormones differentially modulate insulin sensitivity and anabolic lipid metabolism. Additionally, estrogen and progesterone receptors are identified on immune cells,[30] largely suppressing their functions. Estriol is produced by the feto-placental unit and regulates utero-placental blood flow and vascularization, which is likely supported by increased systemic Vascular Endothelial Growth Factor (VEGF).[23]

Box 1. Setpoint change in the immune system: Homeostasis involves a combination of positive and negative feedback systems that balance out to provide an equilibrium (setpoint) to components in a system. Setpoints in the immune system are altered through changes in cell numbers, lifespan, regulatory phenotype (e.g., activator or inhibitory receptors) and secreted effector molecules such anti or pro-inflammatory cytokines. We focus on systemic immune cell numbers (per ml) as these indicate the likelihood of immune cells reaching sites of infection and can be assessed through the blood, a clinically accessible site. There is also a relocation of immune cells to placenta and decidual tissues in pregnancy, therefore total quantification and more precise locational information for immune cells would be beneficial for future research.

Cell Type	1	2	3	NP	1st	2nd	3rd	Likely drivers of cell number alterations
WBC				6,487	7,960	8,710	9,937	Primarily neutrophils and monocytes
Neutrophils				3,710	5,340	6,160	7,080	Estrogen & Progesterone- G-CSF, GM-CSF, ACP5, reduced apoptosis
C. Monocytes				239	286	280	338	
Int. Monocytes				6.9	14.7	15.4	28	Estrogen & Progesterone- GM-CSF, ACP5, reduced monocyte and monoblast apoptosis
NC Monocytes				13.5	15.2	14.2	13.1	
mDCs				23.9	28.3	29.3	23.6	Estrogen & Progesterone- GM-CSF, ACP5
pDCs				8.2	11.7	11.1	10	Estrogen-GM-CSF
T-Regs				66.9	133	120	100	Progesterone-Vitamin D
B-cells				189	178	161	159	
CD4+ T-cells				1014	858	850	860	Lymphocyte decrease is likely a consequence of precursor
CD8+ T-cells				525	455	455	447	commitment to the granulocyte/ macrophage lineage
NK-cells				170	175	147	116	
Platelet				273,000	251,000	230,000	225,000	Hemodilution, aggregation, peripheral consumption
Eosinophils				140	135	150	115	No significant alterations, any drop may be linked to increased precursor commitment to the granulocyte/ macrophage lineage
Basophils				25	20	25	20	

FC: 4, 2, 1.4, NP, -1.4, -2, -4

Table showing the mean number of cells per microliter of blood during pregnancy taken from several studies (supplemental references[51-11]). This table and associated figures are to be considered descriptive and only to be used as an estimate of immune cells alterations, however we are confident this broadly reflects the literature. Mean numbers, rather than ranges, may be more informative for visualizing set-point alterations. The embedded heatmap depicts the fold change (FC) from non-pregnancy levels. NP = non-pregnant, 1st, 2nd, and 3rd = trimesters.

Table 1: **Immune setpoints in pregnancy.**

Interestingly, hormones may also indirectly control the numbers of immune cells, via regulation of GM- and G-CSF. Estrogen was found to enhance GM-CSF in murine studies[31] and although hormones have not directly been linked to G-CSF production, this growth factor peaks in the late follicular phase of the menstrual cycle when estradiol levels rise.[32] Progesterone increases another potent growth factor for the granulocyte/macrophage lineage: uterine produced uteroferrin (ACP5)[33] and inhibits neutrophil apoptosis.[34] This together reveals hormones control phagocyte expansions observed in pregnancy, while being generally immunosuppressive of their function. The immunosuppressive effect of hormones is also likely to be stronger closer to the source of production, primarily the fetal-placental unit. The fetus contributes dehydroepiandrosterone (DHEA), which can be converted to estrogens in the placenta.[35] DHEA can inhibit phagocyte reactive oxygen species production[36] and suggests fetal suppression of innate immune cell activation via an immune-metabolism mechanism. The placenta serves as a new immune organ, orchestrating many of the systemic immunity changes[8,37] as well as physiological changes including to maternal metabolism.[9] Fetal-placental interplay is vital during pregnancy and has been reviewed in detail,[37] here we focus primarily on systemic immune alterations.

In summary, implantation generates an inflammatory environment that is countered by corpus luteum and subsequently placental hormones. This leads to development of a new immune organ and orchestration of changes in homeostasis setpoints, characterized systemically by a shift in lipid homeostasis, immune cell numbers and cytokine levels toward elevated myeloid immune cell subsets at the expense of lymphocytes. From this, we have compiled data from multiple quantitative studies in healthy pregnancy to produce a descriptive figure which details immune cell changes (per ml of blood) in pregnancy (Fig. 1) and proposed the immunomodulators of this immunophenotype (Table 1).

Increased risk of viral sepsis in pregnancy

The numbers of pregnant and peripartum women with severe COVID-19 increased during the UK's second wave, requiring admission to intensive care.[38] These findings reflect the common characteristic for an increased risk of disease severity rather than simply level of infection in pregnancy. This has been reported with many other groups of viruses such as hepatitis E[39] and Ebola virus,[40] indicating that subtle alterations in host immunity may underlay the maladapted response to opportunistic pathogens.

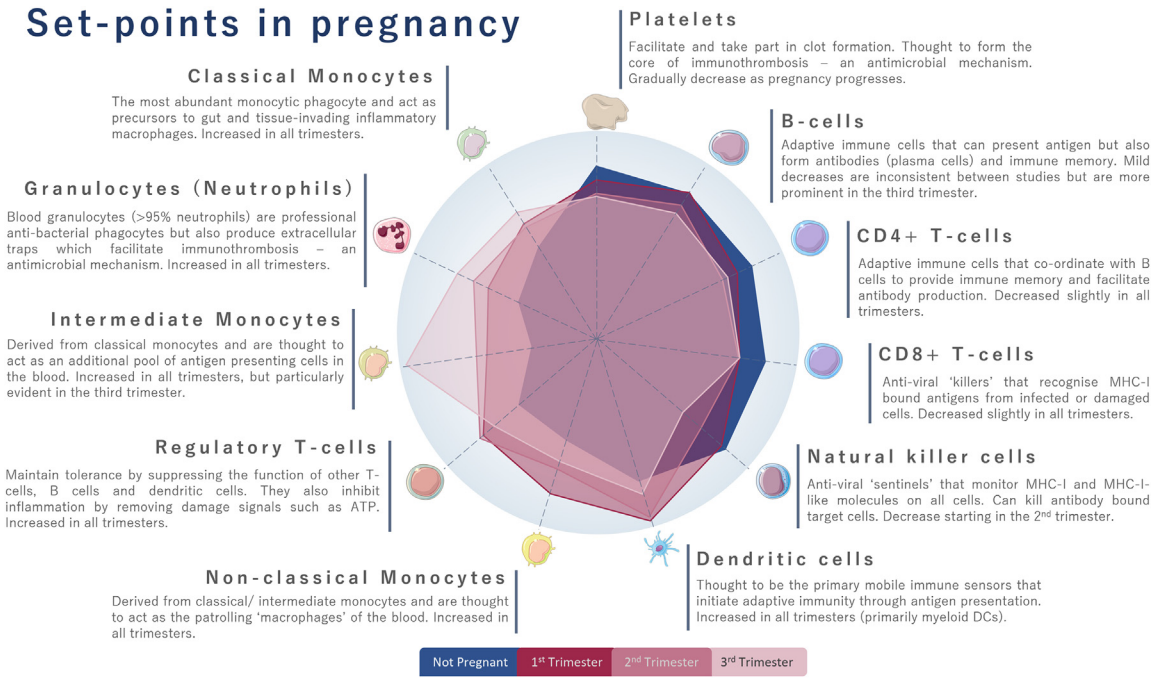

***Fig. 1:* Immune cell setpoint changes in pregnancy.** Spider-web chart showing the relative shift in immune cells per ml of blood during different trimesters of pregnancy. Data was quantified from several studies and based on mean or median cells per microliter of blood, references, data, and method are listed in Table 1. As an appropriate number of data references could not be obtained for raw cell counts, this data format should only be considered descriptive of the changes that occur in pregnancy, however we are confident this figure broadly reflects the literature.

This risk is established in second trimester when a new maternal immune and metabolic setpoint is fully established as evidenced by stabilized cytokine levels, growth factors and cellular profiles from first trimester.[23] Setpoint changes of the immune-response to infection after the first trimester is reflected by a decrease in blood dendritic cells (DCs)[16] representing key professional antigen presenting cells (APCs) that can cross present viral antigens on MHC class I, activating NK and $CD8^+$ T-cells which control viral infections.[41] The second trimester is also characterized by a further reduction in the number of systemic NK cells (10–20%), while $CD8^+$ T-cell numbers remain suppressed (approximately 20%) (Table 1).[16–18] All these declines almost certainly impact the inflammatory-viral infection setpoint from the second trimester onwards. Notably a lower NK cell count is associated with more severe disease.[42] Although lower systemically, these cells are still present in the uterine wall and are vital for maintenance of a healthy pregnancy.[43] As a possible compensatory response to these changes, T-cells and NK cells have enhanced cytokine responses to influenza A in pregnancy that contributes to more severe disease.[44,45] This is true for many viruses and is not consistent with general immune suppression but is indicative of a maladapted response arising from a new setpoint.

Increased bacterial sepsis risk in pregnancy

A severe response to some bacterial infections is more likely in the third trimester. For instance, the risk of invasive listeriosis (a food borne bacterial pathogen) is increased nearly 100-fold (mostly in the third trimester) amongst pregnant women, which can lead to sepsis and death. Listeria can travel through the placenta and can lead to pregnancy loss, stillbirth, or preterm birth.[46] This risk is mirrored by *E. coli* infection, with the source being urinary or genital tract. An explanation for this could be fetal barrier reductions including loss of the mucus plug and weakening of membranes that can result in premature rupture. *Streptococcus pyogenes* (group A *Streptococcus* - GAS), a respiratory tract pathogen, for an unknown reason becomes a dangerous opportunistic pathogen both in pregnancy and postpartum.[47] In addition, group B Streptococcus colonization increases the likelihood of chorioamnionitis, which can have adverse maternal and neonatal outcomes, including sepsis.[48]

Monocytes increase in pregnancy but more notably in the third trimester, where there is a significant expansion of intermediate monocytes (up to 6-fold) (Table 1).[16,18,25] Intermediate monocytes express high levels of HLA-DR rivalling DCs but express a different variety of co-activator and -inhibitory molecules meaning their regulation by cells such as the increased T-reg

pool will be different. It is possible expansion of this subset is an attempt to balance T-reg control over DC antigen presentation.

Neutrophils also increase in concentration (Table 1), and when considering the increase in blood volume, there is an average > 3.5-fold increase in numbers of circulating neutrophils from pre-pregnancy. This bioenergetic demand on the bone marrow may also explain why pregnant women have increased neutrophil immaturity.[49] These cellular changes increase the neutrophil-lymphocyte ratio higher than 3 in third trimester,[16,18] which would usually signify a mild illness. This ratio is important because neutrophils, once activated, suppress the function of lymphocytes such as T-cells.[50]

Along with cell alterations, mothers in the third trimester are under an increased level of physiological stress which can be identified in increased cortisol[51] and lactate levels, the latter of which can be placental-derived. Cortisol acts to maintain an anti-inflammatory immune system, which along with elevated progesterone, estrogens and fetal DHEA, reduce immune defence, particularly in the placenta. Lactate also has immunomodulatory roles, suppressing immune cell activation and expanding T-regs.[52] Another molecule which has a similar effect is vitamin D. Traditionally vitamin D has been viewed as being deficient in pregnancy, however the levels of active vitamin D3 (calcitriol) are increased in pregnancy, at its highest in 3rd trimester. This is thought to occur because the placenta acts as an additional source of calcitriol conversion,[53] which perhaps results in the reduced calcifediol detected in plasma. Calcitriol suppresses B- and T-cell proliferation, promotes a Th1-2 shift and Th17 to T-reg shift, and downregulates proinflammatory cytokines in monocytes.[54] Interestingly, progesterone increases expression of the vitamin D receptor on T-cells[55] further amplifying this effect. This was shown in mouse studies where administration of a progesterone analogue enhanced T-reg production and maintained fetal tolerance.[56] These alterations coincide with increasing fetal demand for nutrients that results in a catabolic state for the mother with increased lipid catabolism, decreased insulin sensitivity, formation of lactate and ketone bodies.[57] Although the role of ketone bodies is not well understood in pregnancy, they can suppress innate immune cell activation and have been proposed as a treatment for maladapted immune responses to viral infections.[58]

All these changes support an altered immune and metabolic setpoint which has elevated both suppressive and activating factors that adaptively regulate homeostasis. These setpoint changes leave vulnerabilities for an unresolved host-response which can be exploited by opportunistic pathogens and may provide key mechanisms underlying the risks of sepsis.

Parturition establishes a postpartum setpoint

Women are also particularly vulnerable to sepsis in the postpartum period. Post-partum infections cause 75,000 deaths each year with high associated morbidity.[59] Despite preventive measures, including antibiotic use and hospital sanitation efforts, the past two decades have seen a re-emergence of GAS sepsis worldwide.[60] The sepsis risk post-partum is associated with barrier failure during and after parturition. The causes of this failure include widening of the cervix and birth trauma including perineal tearing/episiotomy. One study revealed that the common factor in post-partum maternal sepsis was perineal damage.[61] However, this does not explain how the host response to certain pathogens become maladapted in pregnancy. Here we examine immune changes at this transition and the associated sepsis risk.

The maternal immune setpoint is maintained up until the last few weeks of pregnancy where a new pro-inflammatory environment is formed as the mother prepares for birth.[24] These changes mark late pregnancy and early lactation and are coupled to changes in adipose tissue that starts to break down to generate fatty acids and glycerol. This process of lipolysis regulated through hormonal changes around parturition provides a vital source of energy for meeting increased bioenergetic demands. The precise physiological signal(s) that induce labour are not known although immunometabolism may be a key determinant, as premature labour is associated with infection[62] and integrated trajectories of the maternal metabolome, proteome, and immunome can predict labour onset.[63] The triggering of Toll Like Receptors or cell damage can release pro-inflammatory cytokines, which promote contraction of the uterus, expulsion of the baby, and placental rejection.[20] IL-8, IL-1β, IL-6 and TNF production increase in the cervix to facilitate early cervical ripening and progression of labour.[62] IL-6 increases expression of COX2 releasing PGE_2, often used as a topical agent for ripening the cervix.[64] Supporting this, studies from non-human primates has shown that a strong immune response to infection (IL-6, PGE_2) results in premature labour.[65]

Parturition, or birth, is characterized by an influx of inflammatory immune cells.[62] The inflammation could be a response to a stretched placental and fetal demand for nutrients, which would release danger signals or reduced fetal hormones. Progesterone and estrogens begin to decrease in very late third trimester and progesterone falls 'functionally' during labour.[66] Progesterone suppresses production of PGE_2.[67] The drop in progesterone levels during labour coincides with the increase in PGE_2, thought to act directly to relax smooth muscle and regulate matrix metalloproteinases (MMPs) that degrade the extracellular matrix.[68] Therefore, the pro-inflammatory environment during labour may be a result of the release of hormonal breaks on

inflammation. This along with elevated phagocyte levels will provide a heightened window of innate immune activity that may be a contributing factor toward a maladapted response.

Sepsis risk is at its highest in the first month postpartum.[69] Once the initial risk passes, it is understood that maternal immunity gradually returns to levels pre-pregnancy – though sepsis is still common in women up to one year postpartum.[69] Monocytes and neutrophils reset to pre-pregnancy numbers by 6 weeks[16] while the T-cell response returns after a few months.[70] However, one study identified a transient boost in numbers of T-cells, NK cell and B cells in the first year postpartum.[17] This may represent the response to sharp decreases in pregnancy hormones and increase in post-partum immunomodulatory hormones such as DHEA (Sulphate).[71] The resurgence and increased potency of lymphocytes may also explain the autoimmune disease relapse post-partum, which can be quite severe especially with rheumatoid arthritis.[72]

Immune cell changes in pregnancy: potential stepping-stones to sepsis

The dysregulated host response in sepsis is characterized by a heightened initial systemic inflammation that results in a suppressed immune system. This does not mean physiological systems are decompensated but reflects a maladaptation which arises from alterations in homeostatic setpoints.[73,74] This setpoint includes elevated/hyperactive myeloid immune cells and reduced lymphocyte numbers. Here we present a descriptive figure of immune changes in late pregnancy and compare this to that recorded in sepsis (Fig. 2). As cell quantification data from maternal sepsis is extremely limited, the sepsis changes are formulated from quantitative studies in non-pregnant adult sepsis patients. Although this has caveats, the direction of immune setpoint changes in pregnancy in part mirrors the changes in sepsis, particularly expansion of intermediate monocytes. Interlinked with cellular observations are physiological changes shared between sepsis and pregnancy, which have been recently reviewed.[1] We have also recently highlighted the bioenergetic state as being one of the cardinal rules for governing the host response in sepsis and is interlinked with governing adaptive homeostasis setpoints and immune trajectories.[74] Intriguingly, the catabolic state that develops in the third trimester is also shared in the sepsis response, particularly the lower insulin sensitivity[75] and increase in cortisol,[51] a catabolic hormone. These observations provide physiological and mechanistic insight for a reduced threshold for transitioning to a maladapted setpoint. This has consequences for immunity and may help predict which patients are more likely to develop sepsis.

A clinical consequence for this similarity is that normal ranges for physiological parameters during pregnancy/postpartum substantially overlap with sepsis[5,76]; including high or low temperatures, increased white cell counts and increased heart/respiratory rate. The phenotypic and metabolic states of innate immune cell subtypes in pregnancy are also elevated above normal non-pregnant levels but to a lesser extent than observed with infection.[77] An exaggerated proinflammatory response is further observed with viral infections in pregnant women and is a hallmark of a maladapted innate-immune response.[45] It is worth noting in this context that sepsis can develop with infections (e.g., pyelonephritis) that clinically cannot explain multiple organ failure.[77]

The notion that the immune and metabolic setpoint in pregnancy can potentially increase the risk for sepsis has relevance more broadly toward understanding how these states may predispose an individual to developing sepsis from an infection. On the other hand, this also invokes the possibility for manipulating the setpoint toward disfavouring a dysregulated host response to infection. One strategy that instructs an immune setpoint change to combat specific infections in pregnancy is vaccination and is discussed in the next section.

Vaccination during pregnancy: pre-setting the immune setpoint to specific pathogens

Vaccines work by lowering the setpoint for immune activation and the rapid expansion of effector cells from immunological memory against a specific pathogen and thereby curtail disease and the potential to develop sepsis from that pathogen. Vaccines in pregnancy are often viewed as a double-edged sword, on one hand they provide extra protection, though the increased immune activity they promote is seen as detrimental to fetal tolerance. However, the success of the influenza and SARS-CoV-2 vaccines has shown that this can be effective and safe if appropriately timed to avoid early pregnancy when rejection risk is the highest. Considering that most infections in pregnancy are brought about by a small group of opportunistic pathogens, vaccines should be produced against these. Such a strategy has been proposed against group A *Streptococcus*[78] and would also be useful for group B *Streptococcus*. This has potential to cut off major risks of sepsis in pregnancy by lowering the setpoint threshold for mounting protective immunity and should be considered a major objective.

The above highlights an established protective role whereby maternal protection indirectly benefits fetal health. However, a recent pre-clinical study highlights the importance of considering how the maternal–fetal dyad functions as a joined immunological unit. In this study, pre-challenged pregnant animals to Listeria,

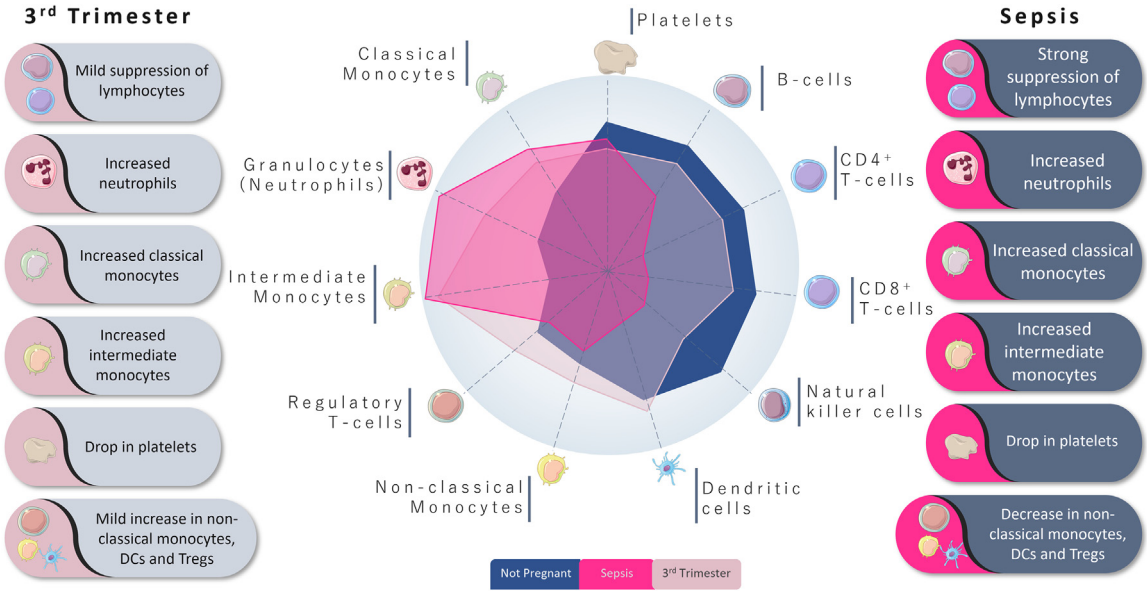

Fig. 2: **Immune cell-type changes in pregnancy: potential intermediate stepping-stones to sepsis.** A spider-web chart depicting relative immune cell-type proportions observed in non-pregnant-individuals, the 3rd trimester of pregnancy and in sepsis patients. To derive a general estimate of cell changes in sepsis and 3rd trimester pregnancy, data was quantified from several studies and based on mean or median cells/ml of blood. Publications, method, and data for 3rd trimester pregnancy are listed in Table 1. Sepsis data has been acquired from non-pregnant female or male patients from multiple studies (per cell type) and made relative to healthy controls (supplemental references[S12-26]).

induce a new post-translational antibody modification mechanism that confers intracellular protection to neonatal mice.[79] Whether this mechanism operates in humans has yet to be shown. Nevertheless, this study has important implications in light of using vaccination as a strategy to re-set the immune-metabolic set-point for the joined maternal–fetal unit.

Outstanding questions

Suppression of immunity in pregnancy is a conviction still held by many clinicians, however, mothers and babies in general are still well protected from pathogens. Nevertheless, in comparison with non-pregnant women, pregnant women are more likely to succumb to a more severe disease, therefore, the subtle alterations in maternal immune and metabolic states contribute to a higher risk of developing sepsis from an infection. Herein we outlined the homeostatic setpoint alterations to the systemic immune system during pregnancy, their interconnections with physiological and metabolic adaptations, and the consequence of these changes for sepsis risk. We conclude that it is the combination of immunomodulatory hormones and enhanced myeloid immune cells which act as a stepping-stone to sepsis rather than a general immune suppression.

Further research is required to investigate these mechanisms including defining what the homeostasis setpoint difference is between pregnant and non-pregnant sepsis? This is likely to be considerable, considering the potent immunomodulatory effects of pregnancy hormones. Also, can this mechanistic understanding help determine key parameters for predicting whether an individual is at risk of developing sepsis? Or can we produce vaccines that inherently work by pre-setting immune setpoints against common sepsis causing pathogens? Hence, further understanding of immune-metabolic setpoints in pregnancy has broader and more general implications that will help lead to better diagnosis and treatments for all.

In relation to changes in homeostasis setpoints, we have emphasised specific immune, metabolic, and hormonal intermediary factors that both determine the underlying immune-metabolic setpoint of the maternal–fetal unit and increase the risk for developing a dysregulated host response in sepsis. We envision that the "right diagnostic tool" for sepsis would use biomarkers that discriminate a maladapted trajectory from a normal homeostatic response to infection.

Finally, the clinical definition of feto-maternal sepsis needs to be refined in order to provide a correct diagnosis and prognosis. For instance, recognising fetal parameters (organ dysfunction) would be important for diagnosing fetal sepsis *in situ*, but would require new tools. Additionally, we believe future tools that quantify the maladapted host response, including immune, metabolic, and hormonal parameters, would reduce the uncertainty in predicting cases of feto-maternal sepsis.

This would require more research and collaboration within the field which will result in better early management and treatments.

Search strategy and selection criteria

Data for this Review were initially selected using Prisma criteria. PubMed and Medline databases were consulted, as well as clinical trials registered in the Cochrane Register from January 1981 to December 2018, using the keywords 'pregnancy', 'immune system' and 'infection' with the search limits of 'human' and 'English'. We focused on primary scientific papers looking at changes in the immune system during the pregnancy period and maternal immune response to infection. 2561 titles were explored, and 80 relevant abstracts were identified. 18 abstracts were excluded as these did not answer the question, and 62 papers were included into the main analysis. Additional studies were identified through cross-referencing and new search terms, (e.g. 'COVID-19' and 'pregnancy') and relevant pre-clinical studies highlighted in the review process. Recent reviews were also included.

Contributors

Author contributions: SS: Conceptualization, Investigation, Writing - Original Draft and Reviewing/Editing. SZ: Conceptualization, Writing - Reviewing and Editing, Project administration, Funding acquisition, Supervision. LCD: Writing - Reviewing and Editing, Investigation, Project administration, Visualization. PDSR: Writing - Reviewing and Editing, Visualization, PG: Conceptualization, Writing - Reviewing and Editing, Project administration, Funding acquisition, Supervision.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2022.104337.

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