Pregnancy: a stepping-stone to sepsis

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Abstract

The physiological shifts during pregnancy predispose women to a ten-fold higher risk of developing sepsis, a life-threatening condition characterised by a maladapted host-response to infection. We present a comprehensive synthesis of maternal immunity during pregnancy, addressing whether altered set-points in immune homeostasis lower the tipping point for sepsis. This close interconnection between maternal immunity and sepsis makes clinical diagnosis highly challenging and translates to delayed antibiotics or overuse. We propose further understanding of the maternal immune set-point changes are vital for tailoring the right diagnostic tools for maternal sepsis and may unravel pathophysiological pathways that predispose an individual to sepsis.

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]. Maternal physiological and immunological adaptations make women more susceptible to sepsis: defined as 'a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or post-partum period[3]'. Mortality rates for COVID-19 are fortunately low in pregnancy, however, the pandemic has had a global impact on 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[4], which has increased numbers of unplanned/unwanted pregnancies due to restricted access to contraception and medical abortions[5]. This together describes a silent surge in maternal sepsis cases, particularly in LMICs, so it is now vital that we understand mechanisms underlying sepsis risk during pregnancy.

Many homeostatic systems with interrelated physiological processes are altered in pregnancy. 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[1,6,7]. Homeostasis of the immune system is also under stringent regulatory control. Against dogma, a woman's immune system is not suppressed, but shifts toward supporting a growing fetus while still defending against infection.

The higher risk for sepsis may be caused by a higher frequency of infections. However, in our review of the literature we find insufficient evidence to support this, but instead find strong evidence for an increased risk for more severe disease (maladapted host response). We discuss insightful studies that have delineated subtle point-changes to the immune system during pregnancy, yet a full mechanistic and functional understanding for maternal health remains challenging. Here, we expose associations between subtle physiological and immune alterations in pregnancy and sepsis and propose that changes in immune homeostasis during pregnancy provide a stepping-stone to sepsis.

Implantation and placentation alter the immune set-point in the first trimester

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[8], including migration of regulatory T-lymphocytes (T-regs) to the uterus[9]. These, along with PD-1 mediated immune checkpoint control[10], create and maintain fetal immune tolerance[11,12]. Subsequently, numbers of T-regs are elevated systemically[13,14] while other T-lymphocytes are decreased by approximately 10-20% in the first trimester (table 1)[15-17]. Mild damage to the endometrium and presence of foreign antigens in implantation primes an inflammatory response which includes upregulation of cytokines such as interleukin 1 and 6 (IL-6, IL-1), and leukaemia inhibitory factor (LIF), the latter being vital for implantation[18]. IL-6 may also increase maternal plasma complement concentrations, especially the pro-inflammatory anaphylatoxins: C3a, C4a, and C5a[19]. In direct response, early embryos counteract this by expressing complement inhibitors and bind to complement regulators, which prevents rejection[20]. After implantation early first trimester is associated with maintained levels of Interferon gamma (IFNγ)[21], tumour necrosis

factor (TNF), alpha defensins (potent antimicrobial compounds)[15], Monocyte Chemoattractant Protein 1 (MCP-1) and growth factors, such as Granulocyte and Granulocyte-Macrophage Colony Stimulating Factors (G-CSF, GM-CSF)[21]. The latter molecules are thought to drive enhanced levels of innate immune cells such as neutrophils (15-75% increased) and monocytes (approximately a 15% increase) in the first trimester (table 1)[15,17,21-25]. Neutrophils can also be preferentially recruited to placental tissues, where high levels of IL-8 have been identified[26], purportedly to protect the fetus from pathogens. Such innate-driven inflammation is becoming recognised a requirement for wound healing processes[27,28], 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 set-point change involves an inhibitory axis driven by increased pregnancy hormones, including the anti-inflammatory progesterone and oestrogens, 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 oestrogens modulate many aspects of maternal physiology including control over metabolism[7]. For instance, both hormones differentially modulate insulin sensitivity and anabolic lipid metabolism. Additionally, oestrogen and progesterone receptors are identified on immune cells[30], largely supressing their functions. Oestriol (the dominant oestrogen) is produced by the feto-placental unit and regulates utero-placental blood flow and vascularisation, which is likely supported by increased systemic Vascular Endothelial Growth Factor (VEGF)[21]. Oestriol is not universally reported as an anti-inflammatory hormone and may have a biphasic effect on cytokine production[31,32]. This coincides with low oestriol at the initial inflammatory phase after implantation, increasing with the progression of pregnancy. Interestingly, oestrogen was found to enhance GM-CSF in murine studies[33]. Antagonistically, progesterone can inhibit GM-CSF production, although it increases another potent growth factor for the granulocyte/macrophage lineage: uterine produced uteroferrin (ACP5)[34]. Additionally, progesterone increases phagocyte numbers by inhibiting apoptosis[35,36]. G-CSF also commits bone marrow precursors to the neutrophil lineage and is produced copiously by decidual tissues[37]. 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 oestradiol levels rise[38]. This together reveals hormones control phagocyte expansions observed in pregnancy, while being generally immunosuppressive. 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 oestrogens in the placenta[39]. DHEA can potently inhibit phagocyte reactive oxygen species production[40] and suggests fetal suppression of innate immune cell activation. The placenta serves as a new immune organ, orchestrating many of the systemic immunity changes[41,42] as well as physiological changes including to maternal metabolism[7]. Fetal-placental interplay is vital during pregnancy and has been reviewed in detail[24,42-44].

Immune set-point changes also consist of potentially overactive immature myeloid cells[45]. Importantly, because of increased tonic GM-CSF signalling, the equilibrium has likely shifted to facilitate release of large numbers upon infection. Given their association with severity of disease[46], expansion of these cells may be a key player for mediating increased severity of the immune response.

In summary, implantation creates 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 set-points, characterised systemically by a shift in immune cell numbers and cytokine levels toward myeloid immune cells at the expense of lymphocytes (detailed in figure 1 and table 1).

Reductions in NK and CD8-T cells characterise the second trimester

Pregnant women were the most vulnerable group during the 1918 influenza pandemic, with a mortality rate between 50 and 75%, and recently were found to be five times more likely to die of H1N1 influenza[47]. Given this maladapted maternal response to viruses, it was logical to presume novel viruses such as SARS-COV-2 (COVID-19) pose a greater risk in pregnancy. Though remarkably, most pregnant women only experienced mild to moderate symptoms and importantly do not appear more likely to contract the infection than the general population[48]. This seems to be a common characteristic for viral infection in pregnancy. Importantly, some studies have found that numbers of pregnant and peripartum women with severe COVID-19 disease increased during the UK's second wave, requiring admission to intensive care and are being considered for supplemental oxygen[49,50]. There is also an increased risk of disease severity with other groups of viruses, indicating that subtle alterations in host immunity may underlay the maladapted response to opportunistic pathogens.

This risk is thought to begin in second trimester when the maternal immune set-point is fully established as evidenced by stabilised cytokines, growth factors and cellular profiles from first the trimester[21]. Maternal serum complement and innate immune cells remain elevated and can lead to enhanced chemotaxis and Ig opsonization to improve maternal defence[44]. However, studies have reported that blood DCs fall from first trimester levels during later stages of pregnancy, starting in the second trimester[15,51,52]. DCs, professional antigen presenting cells (APCs) of the immune system, are highlighted by their innate ability to cross present viral antigens on MHC class I, activating NK and $CD8^+$ T-cells which control viral infections[53]. The second trimester is also characterised by a further reduction in systemic NK cells (10-20%), while $CD8^+$ T-cell numbers remain supressed (approximately 20%) (table 1)[15-17]. All these declines almost certainly negatively impact upon viral protection from the second trimester onwards[11]. Although blood NK cells are reduced, it should be noted that a number of these cells are present in the uterine wall and are vital for maintenance of a healthy pregnancy[54]. Though, these cells are now not readily available to defend the body, including the respiratory tract where maternal infections such as *Streptococcus pyogenes* (group A *Streptococcus* - GAS) originate[55].

Remarkably, considering this data, studies have identified T-cells and NK cells have enhanced cytokine responses to influenza A in pregnancy that contributes to more severe disease[56,57]. This is not consistent with general immune suppression but is indicative of a mismanaged infection, such as that observed in COVID-19[58]. Pregnant women also have a more severe reaction to primary herpes simplex virus[59], varicella zoster virus[60], hepatitis E virus[47], Ebola virus[61] and have significantly reduced interferon production in rhinovirus infection – this change persists up to 6 months post-partum[62]. Type I interferon is an important immune modulator with a protective role during pregnancy and its deficiency affects regulation of the maternal immune system, which in turn results in an altered response to infection[42]. This early lack of an interferon response has been identified in SARS-CoV-2 infection and is usually more

prevalent in men, missing this can lead to a maladapted late interferon response and hyperinflammation[58,63].

Increased risk of bacterial infection and sepsis in the third trimester

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, causing sepsis and death. Listeria can travel through the placenta and can lead to pregnancy loss, stillbirth, or preterm birth[64]. 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. GAS, a respiratory tract pathogen, for an unknown reason becomes a dangerous opportunistic pathogen both in pregnancy and post-partum[55]. This can be explained by the altered immune set-point. The attempt to balance heightened anti-bacterial innate immune activity with suppressive hormones might increase the chance of initially overlooking pathogens which can lead to a hair-triggered innate immune response when the infection is established.

Monocytes increase in pregnancy but more notably in the third trimester, where there is a significant expansion of intermediate monocytes (some report >6-fold) (table 1)[15,17,25,65] and elevation of monocyte activation markers (e.g. CD11b and CD64)[66]. 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-regs pool will be different. It is possible expansion of this subset is an attempt to bypass T-reg control over DC antigen presentation.

Neutrophils also increase in concentration (table 1), and when considering the increase in blood volume[67], there is an average >3.5-fold increase in numbers of circulating neutrophils from pre-pregnancy. This burden on the bone marrow may also explain why pregnant women have increased neutrophil immaturity[45]. These cellular changes increase the neutrophil-lymphocyte ratio higher than 3 in third trimester[15,17,68], which would usually signify a mild illness. This ratio is important because neutrophils, once activated, suppress the function of lymphocytes such as T-cells[69].

Along with cell alterations, mothers in the third trimester are under an increased level of physiological stress which can be identified in increased cortisol[70] and lactic acid levels[71], the latter of which can be placental-derived[72]. These compounds both act to maintain an anti-inflammatory immune system[73,74], which along with elevated progesterone, oestrogens and fetal DHEA, reduce immune defence, particularly in the placenta. Another molecule which has a similar effect is vitamin D (calcitriol), which is increased in pregnancy, but at its highest in 3rd trimester. Vitamin D supresses B- and T-cell proliferation, promotes a Th1-2 shift and Th17 to T-reg shift, and downregulates proinflammatory cytokines in monocytes[75]. Interestingly, progesterone increases expression of the vitamin D receptor on T-cells[76] further amplifying this effect. These alterations coincide with an increasing fetal demand for nutrients that results in a catabolic state for the mother with increased lipid catabolism, decreased insulin sensitivity, formation of lactic acid and ketone bodies[77-79]; the latter of which may be a compensatory mechanism for the drop in anti-viral cells to counteract respiratory viral infections[80].

All these changes support a strained immune set-point which has elevated both suppressive and activating factors to maintain immune homeostasis. This set-point leaves vulnerabilities which can be exploited by opportunistic pathogens and may provide key mechanisms underlying the risks of sepsis.

Parturition and establishment of the postpartum set-point

Pregnant women are vulnerable to sepsis in the postpartum period[81]. Post-partum infections are an important cause of morbidity and mortality in women with 75,000 maternal deaths each year[82]. Despite preventive measures, including antibiotic use and hospital sanitation efforts, the past two decades have seen a re-emergence of GAS sepsis worldwide[83]. 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[84]. However, changes in the pregnancy immune set-point can better explain the maladapted host response to bacteria, especially to the respiratory pathogen GAS.

The maternal immune set-point 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]. It is not clear what physiological signals induce labour, though premature labour is associated with infection[85]. The release of alarmins (danger signals) such as HMGB1[86] or triggering of toll like receptors also lead to cytokine release. Pro-inflammatory cytokines promote contraction of the uterus, expulsion of the baby, and placental rejection[12,18,87]. IL-8, IL-1β, IL-6 and TNF production increase in the cervix to facilitate early cervical ripening and progression of labour[85]. IL-6 and IL-1β increase expression of oxytocin receptors and secretion in myometrial cells. IL-6 also increases expression of COX_2 releasing PGE_2, often used as a topical agent for ripening the cervix[88,89].

Parturition, or birth, is characterized by an influx of inflammatory immune cells[85,90-92]. 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 oestrogens begin to decrease in very late third trimester and progesterone falls 'functionally' during labour[93]. Progesterone suppresses expression of both IL-8 (a neutrophil chemoattractant) and PGE_2[94]. The drop in progesterone levels during labour coincides with the increase in both molecules in the endometrium, which usually promote neutrophil function. However, neutrophils were found not to be required for labour in mouse studies, their function here is primarily thought to be for immune defence and tissue repair[95]. Therefore PGE_2, is thought to act directly to relax smooth muscle or regulate matrix metalloproteinases (MMPs) that degrade the extracellular matrix[96,97]. 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 immune activity that could explain mal-adapted responses.

Once the initial risk of sepsis passes, it is generally understood that maternal immunity gradually returns to levels pre-pregnancy. Specifically, monocytes and neutrophils reset their set-points to pre-pregnancy numbers by 6 weeks[15] while the T-cell response returns after a few months[98,99]. However, one study identified a transient boost in numbers of T-cells, NK cell and B cells in the first year postpartum[16]. This may represent the response to sharp decreases in pregnancy hormones and increase in post-partum hormones such as

dehydroepiandrosterone sulfate[100]. These cell alterations also explain the autoimmune disease relapse post-partum, which can be quite severe especially with rheumatoid arthritis[101].

Pregnancy: a stepping-stone to sepsis

The dysregulated host response in sepsis is characterised by a heightened initial systemic inflammation that results in a supressed immune system[102-104]. This does not mean physiological systems are decompensated but reflects a mal-adaption which arises from alterations in homeostatic set-points[105]. This set-point includes elevated/hyperactive myeloid immune cells and reduced lymphocyte numbers. The direction of these immune set-point changes in part mirrors the changes in pregnancy, particularly expansion of intermediate monocytes (figure 2). Interlinked with cellular observations are physiological changes shared between sepsis and pregnancy, which have been recently reviewed[1]. Additionally, the catabolic state that develops in the third trimester is shared in the sepsis response[106], particularly the drop in insulin sensitivity[107] and increase in cortisol[70], a catabolic hormone. These observations provide physiological and mechanistic insight for a reduced threshold for transitioning to a mal-adapted set-point that 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 systemic inflammatory response syndrome (SIRS) criteria[3,71,108-114] (table 2). SIRS consists of physiological changes that are associated with underlying infection, it is used by many clinicians and referenced by maternal sepsis guidelines[108]. Pregnant women frequently develop SIRS without proof of infection, this is more apparent in labour[108,111]. This can be attributed to suboptimal culture, viral infection, or that bacteria are not necessarily situated in the blood (effects could occur through leakage of pathogen associated molecular patterns). Additionally overwhelming sepsis can develop with infections (i.e. pyelonephritis) that clinically cannot explain development of multiple organ failure[115]. This is a hallmark of innate immune hyper-responsiveness[57] perhaps because of an initial poor response to infection as reported in severe COVID-19[58,63], where there is lack of an early interferon response.

Even with recent proposals for an obstetric early warning system for sepsis[116], there is a frequent under-diagnosis or over-diagnosis of sepsis in the maternal population. The latter is a clinical dilemma considering the rate of inappropriate antibiotic prescriptions in hospitals is estimated at 30 to 50%[117] and can cause allergic reactions, gastrointestinal disturbances, cardiac arrhythmia, antibiotic resistance and death[118]. Additionally, viral sepsis is common in pregnancy[41,119]. Therefore, there is justifiable demand for both maternal specific biomarkers for sepsis and adoption of immunomodulatory drugs, rather than just relying on antibiotics.

The risks of sepsis are not just limited to the immune changes we describe, focus should also be given to individual genetics and the sepsis-causing pathogens themselves. In the UK, ethnic minority groups have a much higher risk of developing sepsis. The reasons for this are still poorly understood, however this can include socioeconomic status, diet, levels of light-induced vitamin D production and other genetic components[120]. Such genetic factors have become apparent in the recent SARS-CoV-2 pandemic where virus receptor ACE2 variants are enriched in certain ethnic groups[121]. Given the risks to ethnic minorities in the UK, it is important that influenza vaccine uptake is promoted in these groups in pregnancy.

Vaccine uptake has been historically low in ethnic minorities[122], though lessons can be learnt from the successful improvement in SARS-CoV-2 vaccine uptake in these groups in the UK.

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. The success of the influenza vaccine however 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 as against group A streptococcus[123]. This has potential to cut off major risks of sepsis in pregnancy by lowering the set-point threshold for mounting protective immunity and should be considered a major objective.

Concluding remarks

Suppression of immunity in pregnancy is a conviction still held by many clinicians, however, even though the risk of sepsis is higher in pregnancy, mothers and babies in general are still well protected from pathogens. Therefore, more subtle alterations must contribute to this risk. Herein we outlined the homeostatic set-point alterations to the systemic immune system during pregnancy, their interconnections with physiological/metabolic adaptations, and the consequence of these changes for sepsis risk. We conclude that it is the combination of immunosuppressive hormones and enhanced myeloid immune cells which act as a stepping-stone to sepsis rather than simply enhanced Th2 immunity or general immune suppression. Further research is required to investigate these mechanisms including differences between pregnant and non-pregnant sepsis. This is likely to be considerable, considering the potent immunomodulatory effects of pregnancy hormones. Further understanding of fine-tuning the immune system in pregnancy will lead to better diagnosis and treatments for all.

Declarations

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. SS and SZ are funded by the Cardiff and Vale University Health Board, PG, LCD, PDSR are funded by the Project Sepsis Ser Cymru Programme from the Welsh Government/European Regional Development Fund. There are no conflicts of interest.

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Boxes

Box 1

Set-point change in the immune system: The changes we describe mark maternal re-adjustments in lymphoid immune homeostasis, allowing for buffering and expansion of the myeloid arm. Homeostasis involves a combination of positive and negative feedback systems that balance out to provide an equilibrium to components in a system. Set-points in metabolism are achieved through positive and negative flux control and substrate availability in pathways. For the immune system, set-points are altered through changes in cell numbers, their regulatory phenotype and secreted effector molecules such cytokines. We have focussed on detectable alterations in the systemic immune system as a clinically accessible site, though notably there is a relocation of immune cells to the placenta and amnion. Nevertheless, we argue the systemic changes are of vital importance because this indicates the likelihood of immune cells reaching sites of infection, though total quantification and more precise locational information for immune cells would be beneficial for the future.

Figures

Figure 1 – Immune cell set-point changes in pregnancy.

Radar plot 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 microlitre of blood, references and data are listed in table 1.

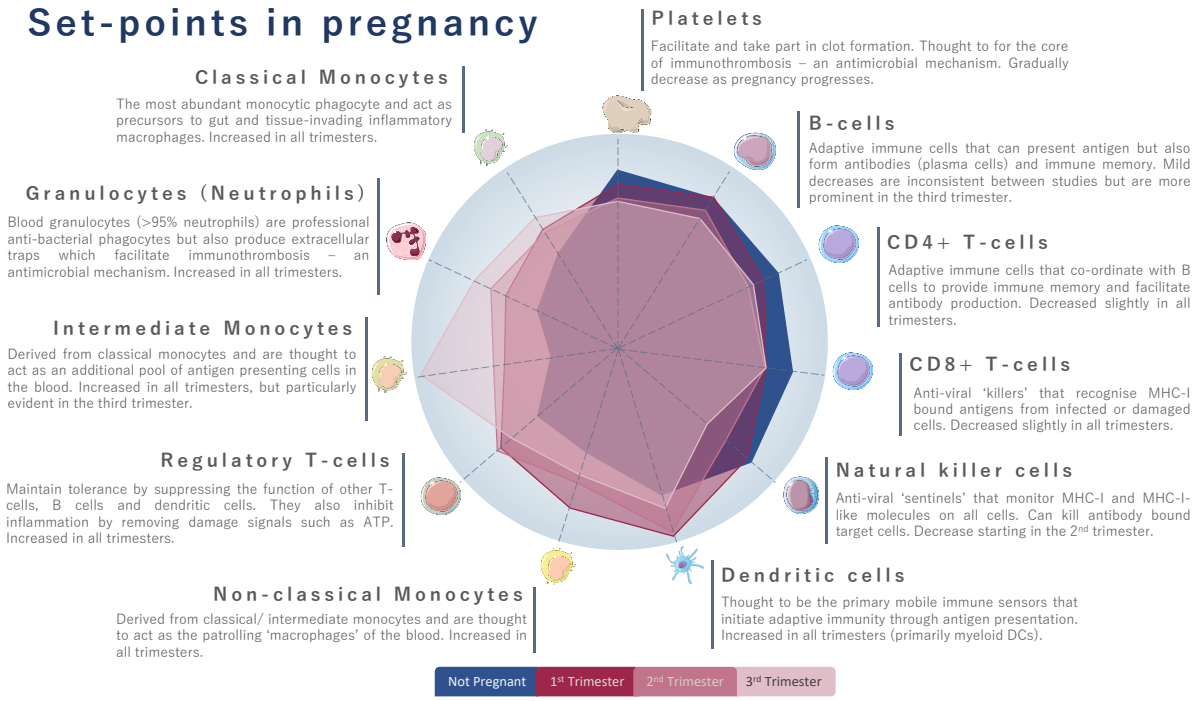
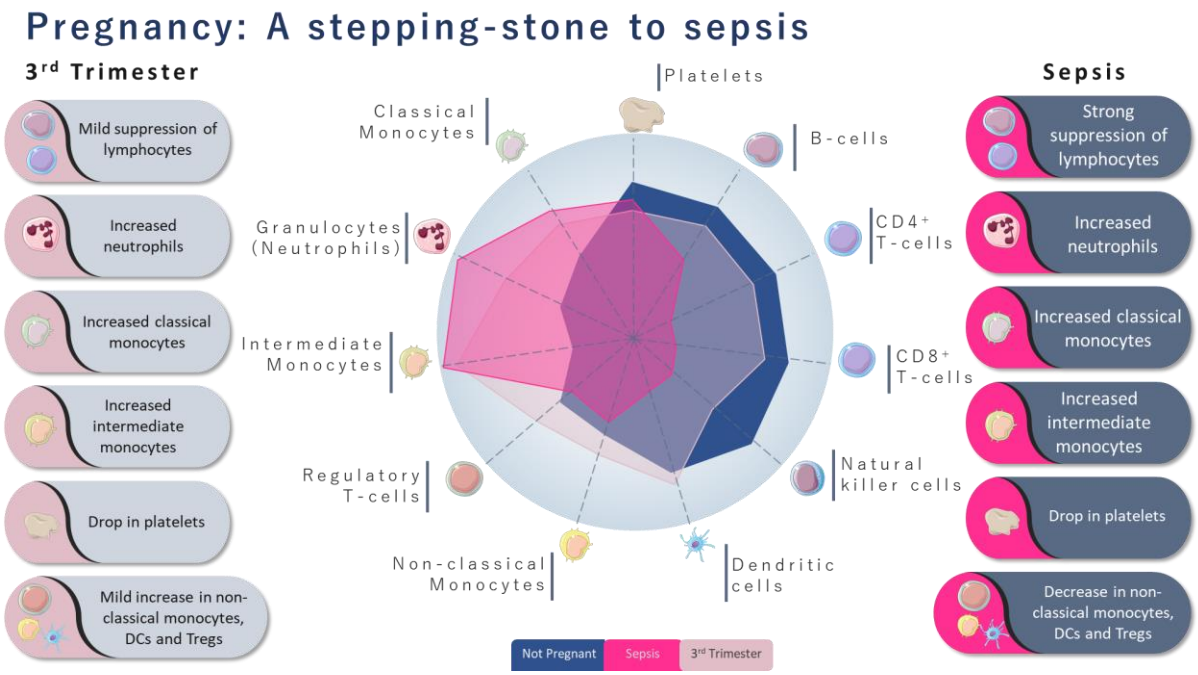


Figure 1 – Pregnancy a stepping-stone to sepsis.

To give a general estimate of cell changes in sepsis and pregnancy, data was quantified from several studies and based on mean or median cells/ml of blood, publications and data for 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[124-138].



Tables

Table 1 Immune set-points in pregnancy.

Table showing the mean number of cells per microlitre of blood during pregnancy taken from several studies. Often cell percentages were combined with WBC, lymphocyte or monocyte counts to obtain approximate final values. The embedded heatmap depicts the fold change (FC) from non-pregnancy levels. NP = non-pregnant, 1st, 2nd and 3rd = trimesters.

Cell Type	Source	1	2	3	NP	1st	2nd	3rd	Likely drivers of cell number alterations
WBC	[68,139,140]				6,487	7,960	8,710	9,937	Primarily neutrophils and monocytes
Neutrophils	[68,139,140]				3,710	5,340	6,160	7,080	Oestrogen & Progesterone- G-CSF[37,38], GM-CSF[33], ACP5[34], reduced apoptosis[36]
C. Monocytes	[17,25,141]				239	286	280	338	
Int. Monocytes	[17,25,141]				6.9	14.7	15.4	28.0	Oestrogen & Progesterone- GM-CSF[33], ACP5[34], reduced monocyte and monoblast apoptosis[142-144]
NC Monocytes	[17,25,141]				13.5	15.2	14.2	13.1	
mDCs	[15,17,51]				23.9	28.3	29.3	23.6	Oestrogen & Progesterone- GM-CSF[33,145], ACP5[34]
pDCs	[15,17,51]				8.2	11.7	11.1	10.0	Oestrogen-GM-CSF[33,145]
T-Regs	[13,14]				66.9	133	120	100	Progesterone-Vitamin D[75,76]
B-cells	[15-17]				189	178	161	159	
CD4+ T-cells	[15-17]				1014	858	850	860	Lymphocyte decrease is likely a consequence of precursor commitment to the granulocyte/ macrophage lineage
CD8+ T-cells	[15-17]				525	455	455	447	
NK-cells	[15-17]				170	175	147	116	
Platelet	[146]				273,000	251,000	230,000	225,000	Haemodilution, aggregation, peripheral consumption[147]
Eosinophils	[139,140]				140	135	150	115	No significant alterations, any drop may be linked to increased precursor commitment to the granulocyte/ macrophage lineage
Basophils	[139,140]				25	20	25	20	

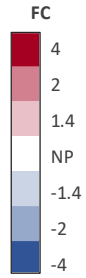
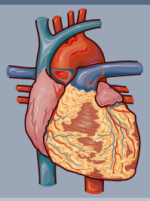
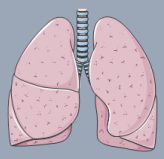
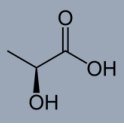


Table 2 – The overlap in physiological changes in pregnancy and labour with SIRS criteria for diagnosing sepsis.

Systemic changes in pregnancy		Systemic changes in SIRS/sepsis
Increase to 70-90 bpm in third trimester, Can increase to theoretical maximum during labour (>180 bpm)		Increase in heart rate over 90 beats per minute
Frequent temperature changes up to 39 °C and below 36 °C during labour		Body temperature >38°C or <36°C
Raised respiratory rate over 20 breaths per minute in labour		Tachypnoea (over 20 breaths per minute)
Raised white cell count Increased granulocyte count Lowered lymphocyte count		Raised white cell count Increased granulocyte count Lowered lymphocyte count
Increased lactic acid to >2mM in labour		Lactic acid >2mM