

Immunological tolerance, pregnancy and pre-eclampsia: the roles of semen microbes and the father¹

^{1,2,3}Louise C. Kenny & ^{4,5*}Douglas B. Kell

¹The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Cork, Ireland, and ²Department of Obstetrics and Gynecology, University College Cork, Cork, Ireland. l.kenny@ucc.ie

³Faculty of Health and Life Sciences, University of Liverpool, Crown St, Liverpool L69 3BX, UK

⁴School of Chemistry, and ⁵The Manchester Institute of Biotechnology, The University of Manchester, 131, Princess St, MANCHESTER M1 7DN, Lancs, UK dbk@manchester.ac.uk

¹ Paper 14 in the series “The dormant blood microbiome in chronic, inflammatory diseases”

Table of contents

Immunological tolerance, pregnancy and pre-eclampsia: the roles of semen microbes and the father	1
Abstract.....	3
Introduction	4
Immune tolerance in pregnancy	5
The clinical course of automimmune disease during pregnancy: an inconsistent effect	6
Mechanisms of immune tolerance during pregnancy	7
Innate and adaptive immunity.....	8
A trade-off for mating and immune defence against infection.....	10
The role(s) of complement in PE	10
Induction of tolerance by exposure to antigens and our main hypothesis: roles of semen and seminal plasma	13
Evidence from epidemiology – semen can be protective against PE	14
The first pregnancy with any given partner means an increased susceptibility to PE	15
Conception early in a new relationship means an increased susceptibility to PE	16
Conception after using barrier contraceptives means an increased susceptibility to PE	16
Conception after using non-barrier methods or after a long period of cohabitation means a decreased susceptibility to PE	17
Donor egg pregnancies have a hugely inflated chance of PE	17
PE in a first pregnancy increases its likelihood in subsequent pregnancies	17
Oral sex with the father is protective against pre-eclampsia in a subsequent pregnancy.....	18
Age is a risk factor for PE.....	18
Donor sperm pregnancies (artificial insemination) are much more likely to lead to PE	18
Evidence from epidemiology – semen can be harmful and can contribute strongly to PE	19
Microbes associated with pre-eclampsia	19
Microbiology of semen.....	22
Roles of the prostate and testes	24
Microbial infections in spontaneous abortions, miscarriages and pre-term birth.....	25
Microbial effects on immunotolerance	25
Effects of vaccination on pregnancy outcomes, including pre-eclampsia.....	26
General or specific?	27
Antimicrobial components of human semen, a part of resistance in the semen microbiome	27
Host tolerance to microbial pathogens.....	27
Sequelae of a role of infection in PE: microbes, molecules and processes.....	28
Placental protein 13 (galectin 1).....	28
Toll-like receptors (TLRs).....	29

Coagulopathies	29
Antiphospholipid syndrome and cardiolipin	29
Treatment options based on (or consistent with) the ideas presented here	31
Conclusions, summary and open questions	32
Acknowledgements	33
Legends to Figures.....	33
References.....	34

Abstract

Although it is widely recognised as involving two stages (poor placentation followed by oxidative stress/inflammation), the precise originating causes of pre-eclampsia (PE) remain elusive. We have previously brought together some of the considerable evidence that a (dormant) microbial component is commonly a significant part of its aetiology. However, apart from recognising, consistent with this view, that the many inflammatory markers of PE are also increased in infection, we had little to say about immunity, whether innate or adaptive. In addition, we focussed on the gut, oral and female urinary tract microbiomes as the main sources of the infection. We here marshal further evidence for an infectious component in PE, focussing on the immunological tolerance characteristic of pregnancy, and the well-established fact that increased exposure to the father's semen assists this immunological tolerance. As well as these benefits, however, semen is not sterile, microbial tolerance mechanisms may exist, and we also review the evidence that semen may be responsible for inoculating the developing conceptus with microbes, not all of which are benign. It is suggested that when they are not, this may be a significant cause of pre-eclampsia. A variety of epidemiological and other evidence is entirely consistent with this, not least correlations between semen infection, infertility and PE. Our view also leads to a series of other, testable predictions. Overall, we argue for a significant paternal role in the development of PE through microbial infection of the mother via insemination.

“In one of the last articles which he wrote, the late Professor F J Browne (1958) expressed the opinion that all the essential facts about pregnancy toxæmia are now available and that all that is required to solve the problem is to fit them together in the right order, like the pieces of a jigsaw puzzle” [1]

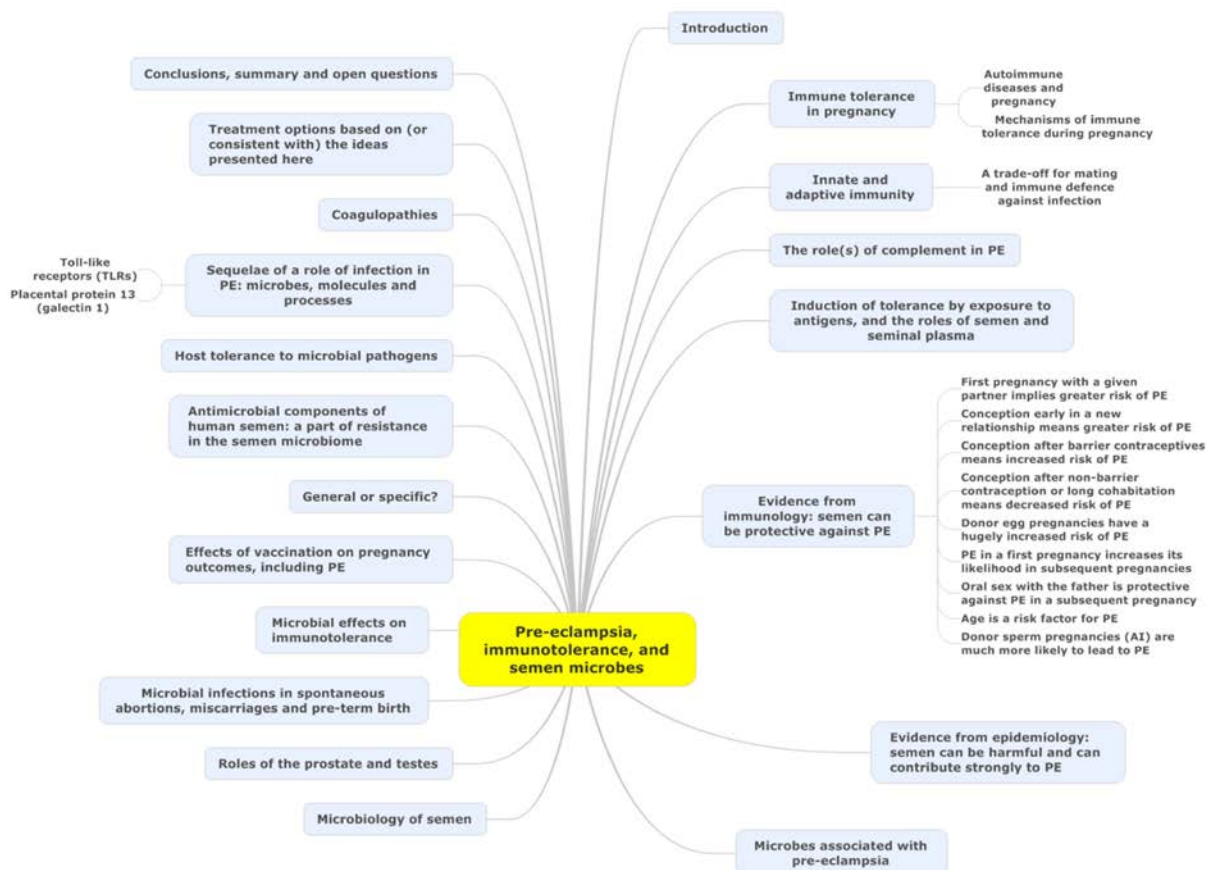
“It appears astonishing how little attention has been given in reproductive medicine to the maternal immune system over the last few decades.” [2]

Introduction

Pre-eclampsia (PE) is a multifactorial disease of pregnancy, in which the chief manifestations are hypertension and proteinuria [3-11]. It affects some 3-5% of nulliparous pregnancies worldwide [10; 12; 13], and is associated (if untreated) with high morbidity and mortality [14-18]. There is much literature on accompanying features, and, notwithstanding possible disease subdivisions [19; 20], the development of PE is typically seen as a ‘two-stage’ process (e.g. [21-27]), in which in a first stage incomplete remodelling of spiral arteries leads to poor placentation. In a second stage, the resulting stress, especially hypoxia-induced oxidative stress [28] (and possibly hypoxia-reperfusion injury), then leads to the symptoms typical of later-pregnancy pre-eclampsia. However, the various actual originating causes of either of these two stages remain obscure. Many theories have been proposed (albeit a unitary explanation is unlikely [19]), and indeed, PE has been referred to as a ‘disease of theories’ [1; 29; 30]. The only effective ‘cure’ is delivery [31], which often occurs significantly pre-term, with its attendant complications for both the neonate and in later life. Consequently, it would be highly desirable to improve our understanding of the ultimate causes of PE, so that better prevention or treatments might be possible.

The ‘two-stage’ theory is well established, and nothing we have to say changes it. However, none of this serves to explain what ‘initiating’ or ‘external’ factors are typically responsible for the poor placentation, inflammation, and other observable features of PE [32].

Microbes are ubiquitous in the environment, and one potential external or initiating factor is low-level microbial infection. In a recent review [32], we developed the idea (and summarised extensive

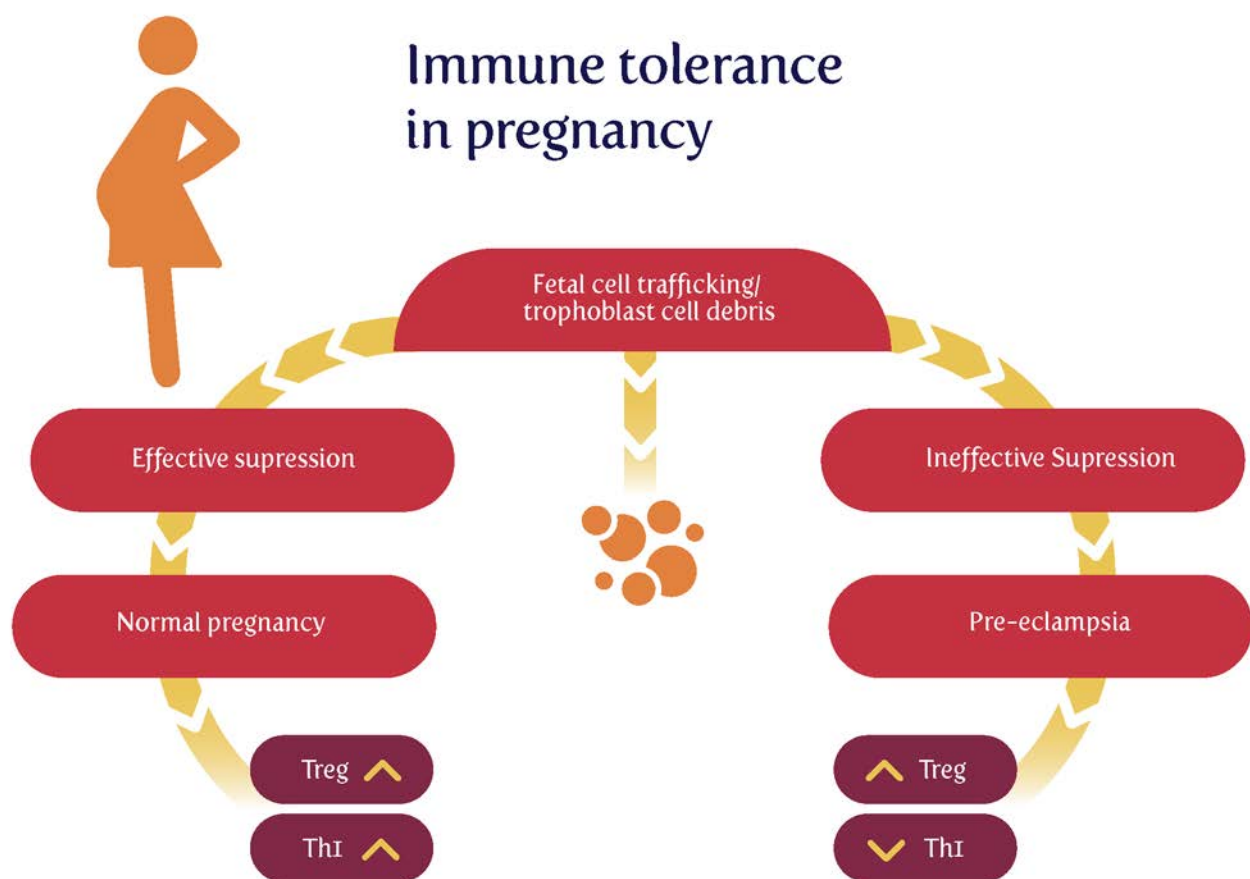


evidence for it) that a significant contributor to pre-eclampsia might be a (largely dormant [33-36] and non-replicating) microbiome within the placenta and related tissues, also detectable in blood and urine. Others (e.g. [37-44]) have drawn similar conclusions. Interestingly, recent analyses [19; 45] of placental gene expression in PE implicate changes in the expression of TREM1 (triggering receptor on myeloid cells-1) and the metalloprotease INHA, and in one case [19] also LTF (lactotransferrin), that also occur during infection [46-49]. Although we highlighted the role of antibiotics as potentially preventative of PE [32], and summarised the significant evidence for that, we had relatively little to say about immunology, and ignored another well-known antidote to infectious organisms in the form of vaccines. There is certainly also an immune component to pre-eclampsia (e.g. [24; 50-58] and below). One of the main theories of (at least part of the explanation of) PE is that of 'immune maladaptation' [50-52; 59]. Thus, the main focus of the present analysis is to assess the extent to which there is any immunological evidence for a role of infectious agents (and the utility of immunotolerance to or immunosuppression of them) in PE. Figure 1 summarises our review in the form of a 'mind map' [60]. We begin with the broad question of immunotolerance, before turning to an epidemiological analysis.

Figure 1. A 'mind map' [60] of the review. Start at 'midnight' and read clockwise.

Immune tolerance in pregnancy

Much of the original thinking on this dates back to Sir Peter Medawar [61-66], who recognised that the paternal origin of potentially half the antigens of the fetus [67] created an immunological conundrum: it should normally be expected that the fetus's alloantigens would cause it to be attacked by the maternal immune system as 'foreign'. There would therefore have to be an 'immune tolerance' [65; 68-70]. Historically it was believed that the fetus is largely 'walled off' from the mother [71]; however, we now appreciate [72; 73] that significant trafficking of fetal material across the placenta into the maternal circulation and vice versa occurs throughout pregnancy. Indeed, this is the basis for the development of non-invasive prenatal testing (NIPT). In line with this, grams of trophoblast alloantigens are secreted daily into the maternal circulation during the third trimester (Figure 2), and this is related to the prevalence of PE [74-80]. Consequently, both the concept and the issue of immune tolerance are certainly both real and important. At all events, the immunobiology of the fetus has been treated in theory largely in the way that a transplanted graft is treated, and uteroplacental dysfunction (leading to PET and IUGR) is largely regarded as a graft rejection (e.g. [53; 81-87]). Clearly there are relationships between the immunogenicity of the foreign agent and the responsiveness of the host; to this end, Zelante and colleagues [88] recognise the interesting similarities between tolerance to paternal alloantigens (as in pregnancy)



and the tolerance observed in chronic fungal infections.

Figure 2. Effective suppression of response to fetal cell trafficking leads to a normal pregnancy, while its failure can lead to pre-eclampsia

The clinical course of automimmune disease during pregnancy: an inconsistent effect

The seminal observation by Philip Hench that the symptoms of the rheumatoid arthritis (RA) were frequently and dramatically ameliorated by several conditions, including pregnancy [89], led to the discovery of cortisone [90] and gave unique insights into the complex interaction between the maternal immune system and the developing fetal/placental unit. Contemporary data suggests that the improvement in RA is not ubiquitous as first thought. Amongst all pregnant women about 25% of women have no improvement in their symptoms at any stage in pregnancy and in a small number of cases the disease may actually worsen [91]. The process by which pregnancy affects disease activity in RA is not completely understood and several putative mechanisms have been proposed. Of interest, although plasma cortisol rises during pregnancy and was initially thought to be key in the amelioration of symptoms, there is actually no correlation between cortisol concentrations and disease state [92]. It has also been reported that the degree of maternal and paternal MHC mismatch has been shown to correlate with the effect of the RA remission during pregnancy [93], leading to the hypothesis that the early immunological events in pregnancy that establish tolerance to the fetal allograft contribute to RA remission. Clearly, this may also account for the disparity in response to pregnancy. RA is not unique in being the only autoimmune disease to be profoundly altered by pregnancy. Although less well studied, non-infectious uveitis tends to improve during pregnancy from the second trimester onwards, with the third trimester being associated with the lowest disease activity [94]. Again, the mechanism underlying this phenomenon is not completely elucidated.

It is now generally accepted [95] that, notwithstanding the sweeping generalisation, autoimmune diseases with a strong cellular (innate) pathophysiology (RA, Multiple Sclerosis (MS)) improve, whereas diseases characterised by autoantibody production such as systemic lupus erythematosus (SLE) and Grave's disease tend towards increased severity in pregnancy.

We have previously reported an association between pregnancy and the risk of subsequent maternal autoimmune disease which was also related to the mode and gestation of delivery. There was an increased risk of autoimmune disease after Caesarean section may be explained by amplified fetal cell traffic at delivery, while decreased risks after abortion may be due to the transfer of more primitive fetal stem cells [96].

Mechanisms of immune tolerance during pregnancy

Following the recognition of maternal immunotolerance, a chief discovery was the choice of HLA-G, a gene with few alleles, for the antigens used at the placental interface. Thus, the idea that placental HLA-G proteins facilitate semiallogeneic pregnancy by inhibiting maternal immune responses to foreign (paternal) antigens via these actions on immune cells is now well established [97-102].

It is also well established that Regulatory T cells (Tregs) play an indispensable role in maintaining immunological unresponsiveness to self-antigens and in suppressing excessive immune responses deleterious to the host [103]. Consequently, much of present thinking seems to involve a crucial role for regulatory Tregs in maintaining immunological tolerance during pregnancy [53; 64; 104-114], with the result that effector T cells cannot accumulate within the decidua (the specialized stromal tissue encapsulating the fetus and placenta) [115].

In an excellent review, Williams and colleagues [116] remark "Regulatory T cells (Tregs) are a subset of inhibitory CD4⁺ helper T cells that function to curb the immune response to infection, inflammation, and autoimmunity". "There are two developmental pathways of Tregs: thymic (tTreg) and extrathymic or peripheral (pTreg). tTregs appear to suppress autoimmunity, whereas pTregs

may restrain immune responses to foreign antigens, such as those from diet, commensal bacteria, and allergens". Their differential production is controlled by a transcription factor called Foxp3.

Further, "a *Foxp3* enhancer, conserved noncoding sequence 1 (CNS1), essential for pTreg but dispensable for tTreg cell generation, is present only in placental mammals. It is suggested that during evolution, a CNS1-dependent mechanism of extrathymic differentiation of Treg cells emerged in placental animals to enforce maternal-fetal tolerance [117]".

Williams and colleagues conclude that "These findings indicate that maternal–fetal tolerance to paternal alloantigens is an active process in which pTregs specifically respond to paternal antigens to induce tolerance. Thus, therapies should aim not to suppress the maternal immune system but rather to enhance tolerance. These findings are consistent with an increase in the percentage of Tregs during pregnancy and with no such increase in women with recurrent pregnancy loss [118]" [116]. Thus maternal tolerance is based on exposure to the paternal alloantigens, although mechanisms such as the haem oxygenase detoxification of haem from degrading erythrocytes [119] are also important. Note too that pregnancy loss is often caused by automimmune activity [120] (and see later).

Additionally, Treg cells have several important roles in the control of infection (e.g. [121-126]). These include moderating the otherwise potentially dangerous response to infection, and being exploited by certain parasites to induce immunotolerance.

Finally, here, it is also recognised that the placenta does allow maternal IgG antibodies to pass to the fetus to protect it against infections. Also, foreign fetal cells persist in the maternal circulation [127] (as does fetal DNA, nowadays used in prenatal diagnosis). One cause of pre-eclampsia is clearly an abnormal immune response towards the placenta. There is substantial evidence for exposure to partner's semen as prevention for pre-eclampsia, largely due to the absorption of several immune modulating factors present in seminal fluid [128]. We discuss this in detail below.

Innate and adaptive immunity

Although they are not entirely independent [129; 130], and both respond to infection, it is usual to discriminate (the faster) innate and (the more leisurely) adaptive immune responses (e.g. [131-135]). As is well known (reviewed recently [136]), the innate immune system is responsible for the recognition of foreign organisms such as microbes. It would be particularly convenient if something in the immune response did actually indicate an infection rather than simply any alloantigen, but unfortunately – especially because of the lengthy timescale over which PE develops – innate responses tend to morph into adaptive ones. This means (i) that there may be specific signals from early innate events that may be more or less specific to innate responses, and (ii) that it also does not exclude the use of particular patterns of immune responsive elements [137-139] to characterise disease states.

A dysregulation of the immune system is widely recognised as an accompaniment to normal pregnancy [64; 111; 140-142], and especially in PE [51; 53; 54; 56-59; 143-150], and it is worth looking at it a little more closely.

The innate immune system responds to microbial components such as LPS via cell membrane receptors. Innate immune cells express a series of evolutionarily conserved receptors known as pattern-recognition receptors (PRRs). PRRs recognise and bind conserved sequences known as pathogen-associated molecular patterns (PAMPs). Bacterial lipopolysaccharide (LPS) and peptidoglycan, and double stranded viral RNA are unique to microbes and act as canonical PAMPs, while the main family of PRRs is represented by the Toll-like receptors (TLRs) [151; 152].

Downstream events, as with many others [153; 154] converge on the NF- κ B system and/or interferon, leading to the release of a series of inflammatory cytokines such as IL-2, IL-6, IL-8, TNF- α and especially IL-1 β .

Matzinger's "danger model" [155-160] (and see [65] and Figure 3) suggested that activation of the immune system could be evoked by danger signals from endogenous molecules expelled from injured/ damaged tissues, rather than simply from the recognition of non-self (although of course in the case of pregnancy some of these antigens are paternal alloantigens). Such endogenous molecules are referred to as Damage-associated molecular patterns (DAMPs), but are not our focus here, albeit they likely have a role in at least some elements of PE [161]. We shall see later, however, that Matzinger's theory is entirely consistent with the kinds of microbial (and disease) tolerance that do seem to be an important part of pregnancy and PE (and see [162]).

The maternal innate immune system plays an important role both in normal pregnancy, and in particular in hypertensive disorders of pregnancy including preeclampsia (PE) [143; 163-169]. One persuasive and widely accepted view is that normal pregnancy is characterised by a low-grade systemic inflammatory response and specific metabolic changes, and that virtually all of the features of normal pregnancy are simply exaggerated in pre-eclampsia [32; 163; 170; 171]. Certainly it is long established that "Normal pregnancy and preeclampsia both produce inflammatory changes in peripheral blood leukocytes akin to those of sepsis" [163], and there are innate Immune defences in the uterus during pregnancy [140]. Normal pregnancy is considered to be a Th2 type immunological state that favours immune tolerance in order to prevent fetal rejection [119]. By contrast, preeclampsia (PE) has been classically described as a Th1/Th2 imbalance [106; 145; 172-174], but as mentioned above (and before [32]), recent studies have highlighted the role of regulatory T-cells as part of a Th1/Th2/Th17 paradigm [143; 144]. This leads to the question of whether there is some kind of trade-off between the responses to paternal alloantigens and those of microbes.

History of Immunological Models

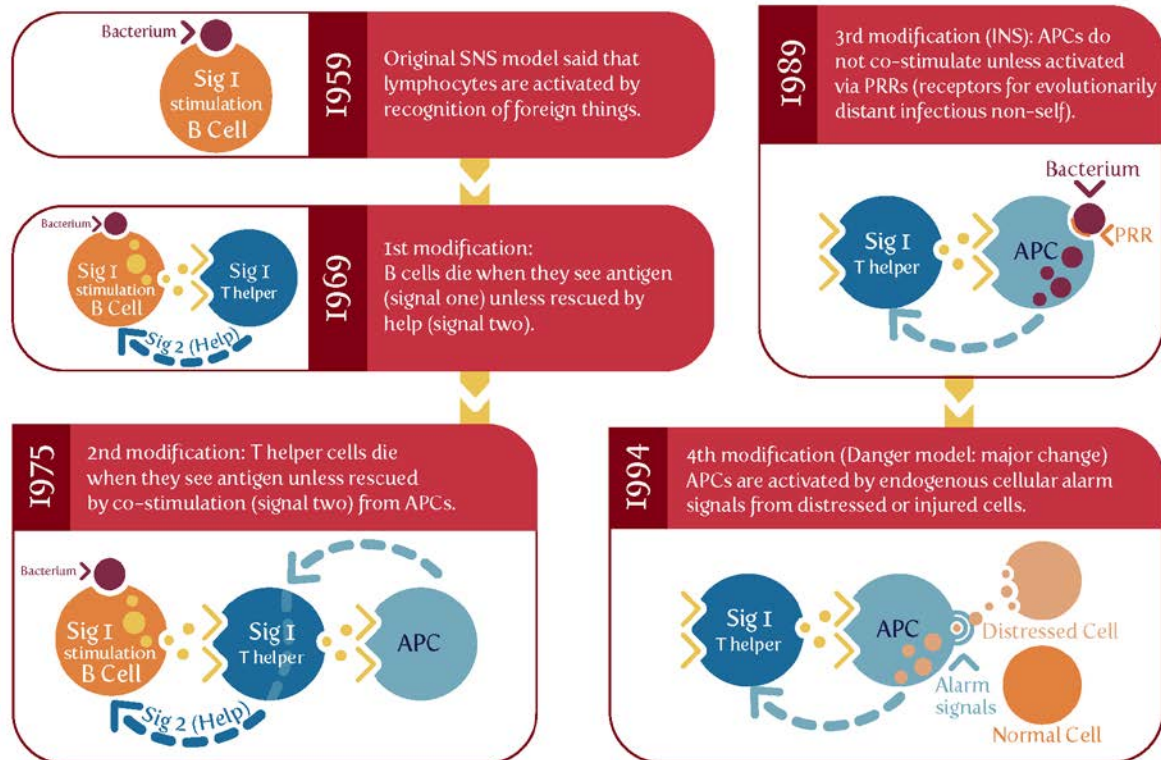


Figure 3. Matzinger's 'danger model' vs the classical theory of self vs self-nonself. Based on and redrawn from [158].

A trade-off for mating and immune defence against infection

Certainly there is some evidence for a trade-off between mating and immune defence against infection [175-177]. Consistent with this (albeit with much else) is the fact [178-180] that pregnancy is associated with an increased severity of at least some infectious diseases. There is evidence [181; 182] that "adaptive immune responses are weakened, potentially explaining reduced viral clearance. Evidence also suggests a boosted innate response, which may represent a compensatory immune mechanism to protect the pregnant mother and the fetus and which may imply decreased susceptibility to initial infection [179]".

The role(s) of complement in PE

Complement, or more accurately the complement cascade, is an important part of the innate immune system that responds to infection. Later (downstream) elements also respond to the adaptive immune system. Our previous review [32] listed many proteins whose concentrations are changed in both infection and PE. Since we regard low-level infection as a major cause of the inflammation observed in PE, one would predict that the complement system is activated in PE, and this observation is amply borne out [183-198]. We give some of the details in Table 1.

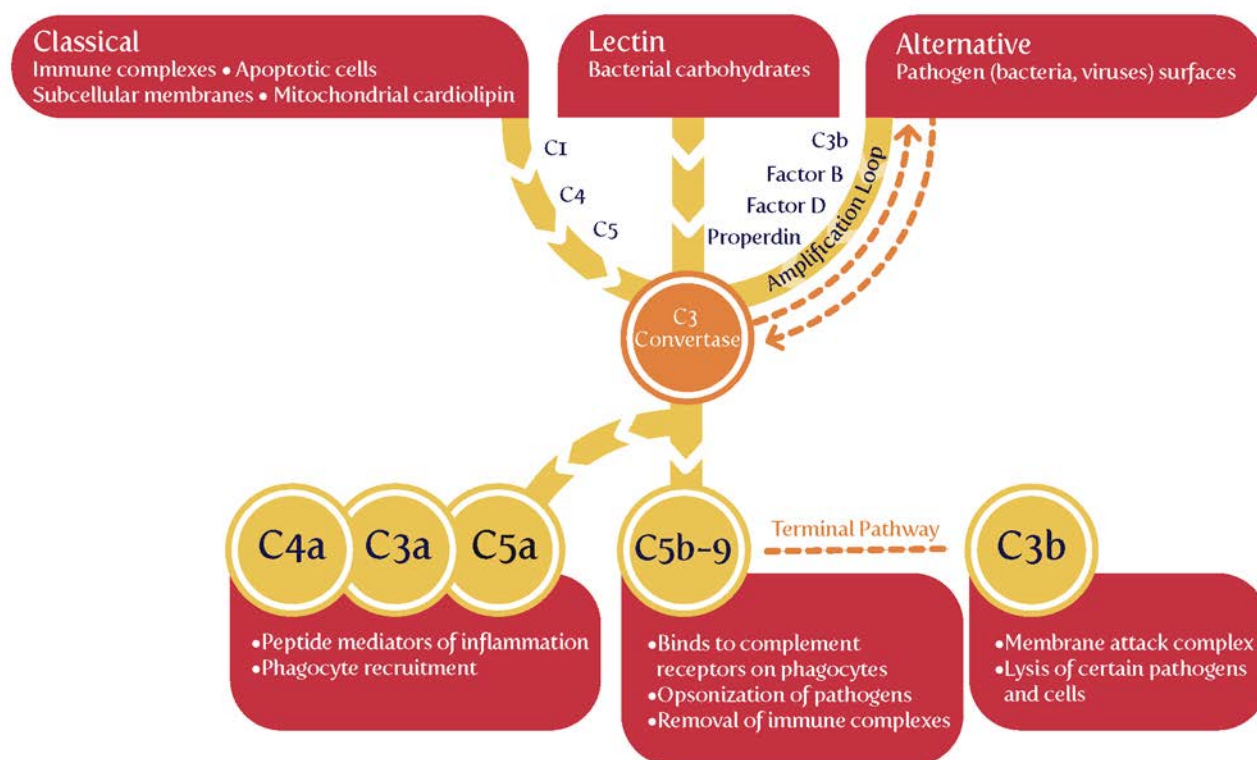


Figure 4. The complement system (based on figures in [135; 188]).

The complement cascade may be activated in three main ways (Fig 4), known as classical, alternative or lectin pathways [130; 186; 188; 199; 200]. Complement activation by the classical, alternative or lectin pathway results in the generation of split products C3a, C4a and C5a with pro-inflammatory properties.

Because both innate and adaptive immunity can activate elements of the downstream complement system, it is hard to be definitive, but there is some evidence that elements such as Ba and Bb (the latter of known structure [201]) are selectively released during infection, very much upstream and in the alternative pathway [188; 199; 200; 202-204]. Most importantly (Table 1), while probably not a specific serum marker, there is considerable evidence that Bb levels are increased in PE, arguably providing further evidence for a role of infectious agents in the aetiology of PE.

Table 1. Changes in the Complement system during PE and related pregnancy disorders

Complement element	Details	Reference
Bb	Raised in PE, OR 2.1 (CI = 1.4–3.1, P < 0.0003)	[185]
Bb	Adjustment for risk factors did not attenuate the association between an elevated Bb and preeclampsia (adjusted odds ratio OR 3.8, 95% CI, 1.6 to 9, P<0.002) in the cohort. After removing women with plasma obtained before 10 weeks, the adjusted OR of Bb in the	[183]

	top decile for preeclampsia was 6.1 (95% CI 2.2 to 17, P<0.0005)	
Bb	Median Bb levels were higher in the maternal plasma of severe PE subjects (n = 24) than in controls (n = 20), 1.45 ± 1.03 versus $0.65 \pm 0.23 \mu\text{g.mL}^{-1}$, $P < 0.001$.	[196]
Bb	Pre-term birth. Women with Bb in the top quartile were 4.7 times more likely to have an SPTB less than 34 weeks' gestation as compared with women who had levels of Bb in the lower 3 quartiles (CI 1.5-14, P<0.003).	[184]
Bb	Maternal Bb levels were significantly higher in the preeclamptic group than in the nonpreeclamptic group (P<0.003 in all studied, P<0.007 in African Americans).	[205]
Bb	Pyelonephritis. Pregnant women with pyelonephritis had a higher median plasma concentration of fragment Bb than those with a normal pregnancy (1.3 mg/ml, IQR: 1.1–1.9 vs. 0.8 mg/ml, IQR: 0.7–0.9; P<0.001). No significant differences were observed in the median maternal plasma concentration of fragment Bb between pregnant women with pyelonephritis who had a positive blood culture and those with a negative blood culture	[206]
Bb	Median amniotic fluid Bb levels were also significantly higher ($P = 0.03$) in preeclamptic women than in normal pregnant women (1127 ng/mL versus 749 ng/mL). The alternative complement pathway is principally involved	[194]
Bb, C3a, C5a, and MAC	Increased significantly in EOSPE (all $P < 0.01$) and LOSPE (P value: 0.027, <0.001, 0.001, and <0.001, respectively) compared with Early/Late control.	[195]. See also [197]
Bb or C3a	Women who were obese with levels of Bb or C3a in the top quartile were 10.0 (95% confidence interval, 3.3–30) and 8.8 (95% confidence interval, 3–24) times, respectively, more likely to develop preeclampsia compared with the referent group at 20 weeks gestation	[207]
C1q and C4d	Increased significantly in LOSPE (P value: .003 and .014, respectively) compared with L-control	[195]. See also [197]
C3a	Adjusted for parity and prepregnancy body mass index, women with levels of C3a in the upper quartile in early pregnancy were three times more likely to have an adverse outcome later in pregnancy compared with women in the lowest quartile (95% confidence interval, 1.8–4.8; $P < .001$). This was especially the case for pre-term birth ($P < .0004$). Elevated C3a as early as the first trimester of pregnancy is an independent predictive factor for adverse pregnancy outcomes, suggesting that complement-related inflammatory events in pregnancy contribute to the subsequent development of poor outcomes at later stages of pregnancy	[188]
C3a	Autoantibody-mediated complement C3a receptor activation contributes to the pathogenesis of preeclampsia	[191]
C3a	Women who developed early-onset preeclampsia as compared with the term pregnant controls had significantly higher ($P = 0.04$) median amniotic fluid C3a levels (318.7 ng/mL versus 254.5 ng/mL)	[194]
C3a	751.6 (194.6–1660) vs 1358 (854.8–2142) ng.mL^{-1} , $P < 0.05$ pre-eclamptic vs healthy pregnant.	[208]

C3a, C3a_desArg & C5a	Elevated at term in PE but not earlier ($P < 0.05$)	[209; 210]
C3a, C5a & AT1-AA	Levels in serum from the severe pre-eclampsia group were significantly higher than in controls ($p < 0.05$).	[211]
C4	C4 was lowered ($P < 0.001$) in serum of term pre-eclamptics	[212]
C4d	Placental immunochemistry showed that C4d was rarely present in placentas from healthy controls (3%), whereas it was observed in 50% of placentas obtained from preeclamptic women ($P = 0.001$)	[190]
C5a	The mean cord plasma C5a concentration was higher in patients with PET ($8.3 \text{ ng/ml} \pm 1.71$) than normal women ($3.2 \text{ ng/ml} \pm 0.35$) $P < 0.01$	[192]
C5b-9	Severe preeclampsia was associated with marked elevations in urinary C5b-9 (median and interquartile range, $4.3 (1.2\text{--}15.1) \text{ ng/mL}$) relative to subjects with chronic hypertension and healthy controls ($P < 0.0001$).	[213]
C6	Novel evidence that genetic variations in complement genes C6 and MASP1- were associated with preeclampsia risk	[198]

We might also note that $C1q^{-/-}$ mice shows features of PE [214], consistent with the view that lowering levels of anti-infection response elements of the complement system leads to PE, consistent again with an infectious component to PE.

Induction of tolerance by exposure to antigens and our main hypothesis: roles of semen and seminal plasma

A number of groups (e.g. [100; 128; 215-218]) have argued for a crucial role of semen in inducing maternal immunological protection, and this is an important part of our own hypothesis here. The second component, however, is a corollary of it. **If it is accepted that semen can have beneficial effects, it may also be that in certain cases it can also have harmful effects.** Specifically, we rehearse the fact that semen is not sterile, and that it can be a crucial source of the microbes that may, over time, be responsible for the development of PE (and indeed other disorders of pregnancy, some of which we rehearse).

Semen consists essentially of the sperm cells suspended in a fluid known as seminal plasma [219]. Seminal plasma contains many components [220; 221], such as transforming growth factor β (TGF- β) [216; 222-224], and there is much evidence that a number of them are both protective and responsible for inducing the immune tolerance observed in pregnancy. Thus, in a key paper on the issue, Robertson and colleagues state, "TGF β has potent immune-deviating effects and is likely to be the key agent in skewing the immune response against a Type-1 bias. Prior exposure to semen in the context of TGF β can be shown to be associated with enhanced fetal/placental development late in gestation. In this paper, we review the experimental basis for these claims and propose the hypothesis that, in women, the partner-specific protective effect of insemination in pre-eclampsia might be explained by induction of immunological hyporesponsiveness conferring tolerance to histocompatibility antigens present in the ejaculate and shared by the conceptus" [128].

TGF β and prostaglandin E (also prevalent in seminal fluid [225]) are potent Treg cell-inducing agents, and coitus is one key factor involved in expanding the pool of inducible Treg cells that react with paternal alloantigens shared by conceptus tissues [226-229].

Both in humans and in agricultural practice, semen may be stored with or without the seminal fluid (in the latter cases, the sperm have been removed from it and they alone are used in the insemination). However, a number of papers have shown very clearly that it is the seminal fluid itself that contains many protective factors, not least in improving the likelihood of avoiding adverse pregnancy outcomes [128; 177; 230; 231]. Thus semen is the preferred substrate for inducing immunotolerance and hence protection against PE.

Evidence from epidemiology – semen can be protective against PE

As well as those (such as pre-existing diseases such as hypertension and diabetes [232; 233], that we covered previously [32]), there are several large-scale risk (or anti-risk) factors that correlate with the incidence of pre-eclampsia. They are consistent with the idea that a woman's immune system adapts slowly to (semen) proteins from a specific male partner [128; 215; 216], and that the content of semen thus has major phenotypic effects well beyond its donation of (epi)genetic material. We believe that our hypothesis about the importance of semen in PE has the merit of being able to explain each of them in a simple and natural way:

1. The first pregnancy with any given partner means an increased susceptibility to PE [5; 234; 235]
2. Conception early in a new relationship means an increased susceptibility to PE [236-238]
3. Conception after using barrier contraceptives means an increased susceptibility to PE [237; 239; 240]
4. Conception after using non-barrier methods or after a long period of cohabitation means a decreased susceptibility to PET [215; 237]
5. Donor egg pregnancies have a hugely inflated chance of PET [235; 241-243]
6. Pre-eclampsia in a first pregnancy increases its likelihood in subsequent pregnancies [244]
7. Oral sex with the father is protective against PE in a subsequent pregnancy [245; 246]
8. Age is a risk factor for PE [247-251].

9. Donor sperm pregnancies (artificial insemination) are much more likely to lead to PE [246; 252-255]

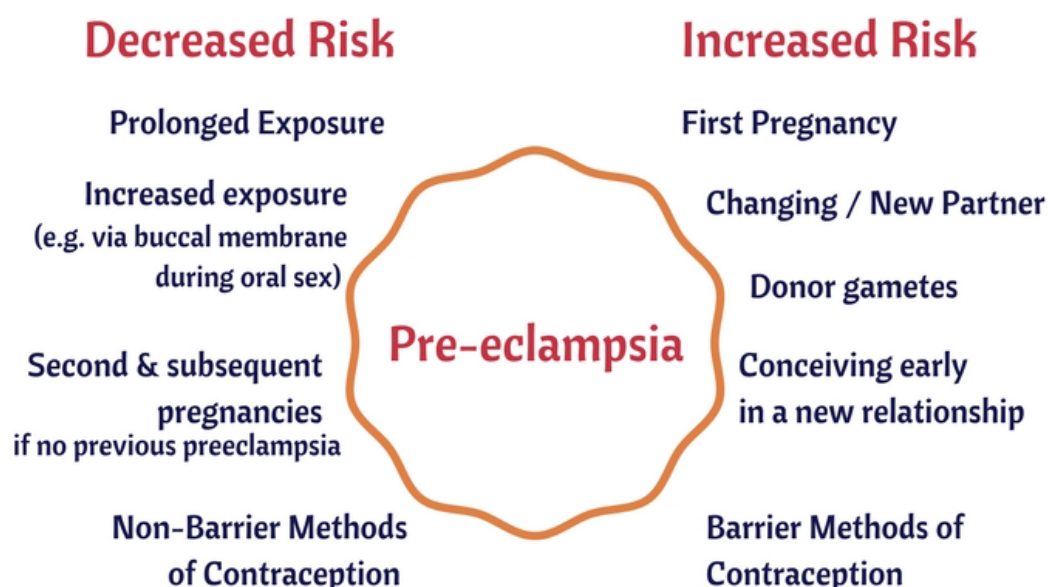


Figure 5. Some epidemiological risk factors for pre-eclampsia

We consider each in turn (Figure 5).

The first pregnancy with any given partner means an increased susceptibility to PE

This is extremely well established (e.g. [5; 54; 149; 232; 234; 235; 256-263]). Thus, Duckitt and Harrington [232] showed nulliparity to have a risk ratio (over pregnant women with previous pregnancies) of 2.91 (95% CI 1.28-6.61). Luo *et al.* [259] find an odds ratio of 2.42 (95% CI 2.16-2.71) for PE in primiparous vs multiparous women, while Deis and colleagues found the OR to be 2.06 (CI 1.63–2.60), $p=0.0021$. Dildy and colleagues [264] summarise several studies, including a very large one by Conde-Agudelo and Belizán [265] (RR 2.38; 95% CI 2.28-2.49), while the meta-analysis of English and colleagues [262] gives a risk ratio for nulliparity of 2.91 (CI 1.28–6.61). The consistency of each of these studies allows one to state with considerable confidence that there is a 2-3-fold greater chance of PE with a first baby.

However, an additional and key clue here is not simply (and maybe even not mainly) that it is just being nulliparous (i.e. one's first pregnancy) but that it is primipaternity – one's first pregnancy with a given father – that leads to an increased susceptibility to PE [183; 266-277] (cf. [278]). Changing partners effectively 'resets the clock' such that the risk with a new father is essentially as for first pregnancies. Thus, Lie *et al.* [279] noted that if a woman becomes pregnant by a man who has already fathered a pre-eclamptic pregnancy in a different woman her increased risk of developing pre-eclampsia is 1.8-fold (CI 1.2-2.6). This is far greater than the typical incidence of PE, even for nulliparous women. The equivalent figure in the study of Lynch and colleagues [183] was RR = 5.1, 95% CI, 1.6 to 15. The strong implication of all of this is that the father can have bad effects but that some kind of 'familiarity' with the partner is protective [275], the obvious version – and that more or less universally accepted – being an immunological familiarity (i.e. tolerance). Note, however, that this is when the pregnancy goes to term: a prior birth confers a strong protective effect against preeclampsia, whereas a prior abortion confers only a weaker protective effect [235].

Conception early in a new relationship means an increased susceptibility to PE

The idea that conception early in a new relationship means an increased susceptibility to PE follows immediately from the above. The landmark studies here are those of Robillard and colleagues [236], of Einarsson and colleagues [237], and of Saftlas and colleagues [238],

Robillard *et al.* [236] studied 1011 consecutive mothers in an obstetrics unit. The incidence of pregnancy-induced hypertension (PIH) was 11.9% among primigravidae, 4.7% among same-paternity multigravidae, and 24.0% among new-paternity multigravidae. For both primigravidae and multigravidae, the length of (sexual) cohabitation before conception was inversely related to the incidence of PIH ($P < 0.0001$).

Einarsson and colleagues [237] studied both the use of barrier methods and the extent of cohabitation prior to pregnancy. For those (allegedly...) using barrier methods before insemination, the odds ratio for PE when prior cohabitation was only 0-4 months versus the odds ratio for PE: normotensive was 17.1 (CI 2.9-150.6), versus 1.2 (CI 0.1-11.5) when the period of cohabitation was 8-12 months, and 1.0 for periods of cohabitation exceeding one year.

Saftlas *et al.* [238] recognised that parous women who change partners before a subsequent pregnancy appear to lose the protective effect of a prior birth. In a large study (mainly based around calcium supplementation), they noted that women with a history of abortion who conceived again with the same partner had nearly half the risk of preeclampsia (adjusted odds ratio = 0.54, 95 percent confidence interval: 0.31, 0.97). In contrast, women with an abortion history who conceived with a new partner had the same risk of preeclampsia as women without a history of abortion (adjusted odds ratio = 1.03, 95 percent confidence interval: 0.72, 1.47). Thus, the protective effect of a prior abortion operated only among women who conceived again with the same partner

Conception after using barrier contraceptives means an increased susceptibility to PE

A prediction that follows immediately from the idea that paternal antigens in semen (or seminal fluid) are protective is that the regular use of barrier methods will lower maternal exposure to them, and hence increase the likelihood of PE. This too is borne out [237; 239; 240]. Thus Klonoff-Cohen and colleagues found a 2.37-fold (CI 1.01-5.58) increased risk of preeclampsia for users of contraceptives that prevent exposure to sperm. A dose-response gradient was observed, with increasing risk of preeclampsia for those with fewer episodes of sperm exposure. Similarly, Hernández-Valencia and colleagues [240] found that the odds ratio for preeclampsia indicated a 2.52-fold (CI 1.17-5.44, $P < 0.05$), increased risk of preeclampsia for users of barrier contraceptives compared with women using nonbarrier contraceptive methods.

Conception after using non-barrier methods or after a long period of cohabitation means a decreased susceptibility to PE

This is the flip side of the studies given above (e.g. [236-238]). It is clear that maternal–fetal HLA sharing is associated with the risk of preeclampsia, and the benefits of long-term exposure to the father's semen, while complex [280], seem to be cumulative [281]. Thus, short duration of sexual relationship was more common in women with preeclampsia compared with uncomplicated pregnancies (≤ 6 months 14.5% versus 6.9%, adjusted odds ratio (aOR) 1.88, 95% CI 1.05–3.36; ≤ 3 months 6.9% versus 2.5%, aOR 2.32, 95% CI 1.03–5.25 [282]. Oral contraceptives are somewhat confounding here, in that they may either be protective or a risk factor depending on the duration of their use and the mother's physiological reaction to them [283].

Donor egg pregnancies have a hugely inflated chance of PE

If an immunological component is important to PE (as it evidently is), it is to be predicted that donor egg pregnancies are likely to be at much greater risk of PE, and they are (e.g. [235; 241-243; 284-288]) (and also of pre-term birth [289]). Thus, Letur and colleagues [241; 242] found that preeclampsia was some fourfold more prevalent using donated eggs (11.2% vs. 2.8%, $P < 0.001$), while Tandberg and colleagues [235] found that various 'assisted reproductive technologies' had risk ratios of 1.3 (1.1–1.6) and 1.8 (1.2–2.8) in second and third pregnancies, respectively. Pecks and colleagues studied pregnancy-induced hypertension (PIH, not just PE) and found that the calculated odds ratio for PIH after oocyte donation, compared to conventional reproductive therapy, was 2.57 (CI 1.91–3.47), while the calculated odds ratio for PIH after oocyte donation, compared to other women in the control group, was 6.60 (CI 4.55–9.57). Stoop and colleagues [290] found a Risk Ratio of 1.502 (CI 1.024-2.204) for PIH. In a study by Levron and colleagues [291], adjustment for maternal age, gravidity, parity, and chronic hypertension revealed that oocyte donation was independently associated with a higher rate of hypertensive diseases of pregnancy ($P < 0.01$). In a twins study, Fox and colleagues [292] found, on adjusted analysis, that the egg donation independently associated with preeclampsia (aOR 2.409, CI 1.051-5.524). The meta-analysis of Thomopoulos and colleagues [293] gave a risk ratio for egg donation of 3.60 (CI 2.56–5.05) over controls, a value similar to that of Blázquez and colleagues [294]. Finally, a recent meta-analysis by Masoudian and colleagues [287] found that the risk of preeclampsia is considerably higher in oocyte-donation pregnancies compared to other methods of assisted reproductive technology (odds ratio, 2.54; CI 1.98-3.24; $P < 0.0001$) or to natural conception (odds ratio, 4.34; CI 3.10-6.06; $P < 0.0001$). The incidence of gestational hypertension and preeclampsia was significantly higher in ovum donor recipients compared with women undergoing autologous IVF (24.7% compared with 7.4%, $P < 0.01$, and 16.9% compared with 4.9%, $P < 0.02$ [295]. All of these are entirely consistent with an immune component being a significant contributor to PE. One obvious question pertains to whether the use of antibiotics assists the progression of IVF. Unfortunately this question has been little researched in humans [296].

PE in a first pregnancy increases its likelihood in subsequent pregnancies

This too is well established: a woman who has had preeclampsia has an increased risk of preeclampsia in subsequent pregnancies [263; 297], especially if suffering from hypertension [298]. This may be seen as relatively unsurprising, and of course bears many explanations, and the increased risks can be very substantial [244]. In the overall analysis of English and colleagues [262], the risk ratio was 7.19 (CI 5.85–8.83). Other examples give the recurrence risk, overall, as some 15% to 18% [263]. The risk of recurrent preeclampsia is inversely related to gestational age at the first delivery, and in the study of Mostello and colleagues [299] was 38.6% for 28 weeks' gestation or earlier, 29.1% for 29-32 weeks, 21.9% for 33-36 weeks, and 12.9% for 37 weeks or more. Low birthweight in the first pregnancy is an independent predictor of PE in the second: birth weight below the tenth percentile in the first delivery accounted for 10% of the total cases of

preeclampsia in the second pregnancy and 30% of recurrent cases [300]. From the perspective developed here, the suggestion is that whatever is responsible for PE in one pregnancy can 'live on' in the mother and afflict subsequent ones. One thing that can 'live on' is a dormant microbial community.

Oral sex with the father is protective against pre-eclampsia in a subsequent pregnancy

Oral sex (with the father of one's baby) protects against pre-eclampsia [245; 246] ($p=0.0003$), arguably because exposure to the paternal antigens in the seminal fluid have a greater exposure to the blood stream via the buccal mucosa than they would via the vagina. This is a particularly interesting (and probably unexpected) finding, that is relatively easily understood from an immunological point of view, and it is hard to conceive of alternative explanations. (Note, however, that in the index study [245], the correlation or otherwise of oral and vaginal sex was not reported, so it is not entirely excluded that more oral sex also meant more vaginal sex.)

Age is a risk factor for PE

Age is a well known risk factor for PE [247-251], and of course age is a risk factor for many other diseases, so we do not regard this as particularly strong evidence for our ideas. However, we have included it in order to note that age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction [301].

Donor sperm pregnancies (artificial insemination) are much more likely to lead to PE

Finally, here, turning again to the father, it has been recognised that certain fathers can simply be 'dangerous' in terms of their ability to induce PE in those who they inseminate [277; 302]. By contrast, if immunotolerance to a father builds up slowly as a result of cohabitation and unprotected sex, a crucial prediction is that donor sperm pregnancies will not have this property, and should lead to a much greater incidence of PE. This is precisely what is observed [246; 252-255; 284].

In an early study [252], Need and colleagues observed that the overall incidence of PE was high (9.3%) in pregnancies involving artificial insemination by donor (AID) compared with the expected incidence of 0.5-5.0%. The expected protective effect of a previous pregnancy was not seen, with a 47-fold increase in PE (observed versus expected) in AID pregnancies after a previous full-term pregnancy. That is a truly massive risk ratio.

Smith and colleagues [253] compared the frequency of PE when AI was via washed sperm from a partner or a donor, finding a relative risk for PE of 1.85 (95% CI 1.20 - 2.85) for the latter, and implying that the relevant factor was attached to (in or on) the sperm themselves.

In a similar kind of study, Hoy and colleagues found [254], after adjusting for maternal age, multiple birth, parity and presentation, that 'donor sperm' pregnancies were more likely to develop pre-eclampsia (OR 1.4, 95% CI 1.2-1.8).

Salha and colleagues [284] found that the incidence of pre-eclampsia in pregnancies resulting from donated spermatozoa was 18.2% (6/33) compared with 0% in the age- and parity-matched partner insemination group ($P < 0.05$).

Wang *et al.* [303] found that the risk of pre-eclampsia tripled in those never exposed to their partner's sperm, i.e. those treated with intracytoplasmic sperm injection done with surgically obtained sperm.

In a study of older women, Le Ray and colleagues [304] noted that the pre-eclampsia rate differed significantly between various groups using assisted reproductive technology (3.8% after no IVF, 10.0% after IVF only and 19.2% after IVF with oocyte donation, $P < 0.001$).

Davis and Gallup reviewed what was known in 2006 [255], particularly from an evolutionary point of view, concluding that one interpretation of PE was that it was the mother's way of removing 'unsuitable' fetuses. This does not sit easily with the considerable mortality and morbidity associated with PE pre-delivery, especially in the absence of treatment. However, Davis and Gallup [255] did recognise that "pregnancies and children that result from unfamiliar semen have a lower probability of receiving sufficient paternal investment than do pregnancies and children that result from familiar semen", and that is fully consistent with our general thinking here. Bonney draws a similar view [162], based on the 'danger' model [156; 158], that takes a different view from that of the 'allograft' or 'self-nonsel self discrimination' model. In the 'danger model', the decision to initiate an immune response is based not on discrimination between self and non-self, but instead is based on the recognition of 'danger' (abnormal cell death, injury or stress). One such recognition is the well-established recognition of microbes as something likely to be causative of undesirable outcomes.

In the study of González-Comadran and colleagues, [305], conception using donor sperm was again associated with an increased risk of preeclampsia (OR 1.63, 95% CI 1.36–1.95).

Thomopoulos and colleagues carried out two detailed and systematic reviews [293; 306]; the latter [293] covered 7,038,029 pregnancies (203,375 following any invasive ART) and determined that the risk of PE was increased by 75% (95% CI, 50%–103%).

Overall, these studies highlight very strongly indeed that the use of unfamiliar male sperm is highly conducive to PE relative to that of partner's sperm, especially when exposure is over a long period. We next turn to the question of why, in spite of this, we also see PE even in partner-inseminated semen, as well as more generally.

Evidence from epidemiology – semen can be harmful and can contribute strongly to PE

In our previous review [32], we rehearsed the evidence for a considerable placental and vaginal microbiome, but did not discuss the semen microbiome at all. To repeat, therefore, the particular, and essentially novel, part of our hypothesis here is that **if it is accepted that semen (and seminal plasma) can have beneficial effects, it should also be recognised that in certain cases it can also have harmful effects.** In particular, we shall be focussing on its microbial content (we ignore any epigenetic effects [307]). We note that this idea would fit easily with the recognition that as well as inducing tolerance to paternal antigens, exposures to the father's semen can build tolerance (immunity) to its microbes, thereby decreasing the risk of PE. However, microbes and their associated PAMPs are well known to be highly inflammatory, whether or not they are reproducing, and we consider that it is this that is likely the particular driver of the sequelae observable in PE.

Microbes associated with pre-eclampsia

The female's urogenital microbiome is important in a number of pregnancy disorders [44; 308-310]. Specifically, we previously found many examples in which microbes are associated with PE, and we here update the CC-BY-licensed Table 2 thereof [32] as Table 2 here:

Table 2. Many studies have identified a much greater prevalence of infectious agents in the blood or urine or gums of those exhibiting PE than in matched controls

Microbes	Comments	Reference
<i>Chlamydia pneumoniae</i>	IgG seroprevalence and gDNA	[311]

	associated with PE (P<0.0001)	
	IgG (but not IgA or IgM) associated with PE, OR = 3.1.	[312]
	Significantly greater numbers with PE, and reversion under antichlamydial treatment	[313]
	Much greater incidence (P<0.006)	[314]
	OR 4.1; P <0.02 for association with PE (15/48 cases vs 3/30 controls)	[315]
<i>Chlamydia trachomatis</i>	Increased risk of PE, OR = 7.2 or 1.6 based on serology	[316; 317]
Cytomegalovirus	RR for PE 1.5 if infected with CMV	[318] (see also [319])
<i>Helicobacter pylori</i>	Seropositivity or DNA. OR=2.7, or 26 if CagA seropositivity	[320] and editorial [321]
	IgG seropositivity 54%PE vs 21% controls	[314]
	Anti-CagA antibodies cross-react with trophoblasts and could inhibit placentation	[322]
	2.8x greater seropositivity in PE group	[323]
	OR=2.86 for seropositivity in PE, correlated with high malondialdehyde levels	[324]
	Wide-ranging review of many studies showing PE more prevalent after <i>Hp</i> infection	[325]
	Seropositivity PE:control = 84%:32% (P<0.001)	[326]
	OR for seropositivity 1.83 (P<0.001)	[327]
	Seropositivity PE:control 86%:43% (P<0.001)	[328]
	Massive increase in seropositivity in women with PE	[329]
	Seroprevalence (57%) > controls (33.%) (P<.001). Seropositivity for CagA-positive strains 45.2% in preeclamptic women vs 13.7% in controls (P<.001). Infection associated with abnormalities of uterine arteries	[43]
	Much greater incidence of antibodies to <i>H. pylori</i>	P<0.0001
Human immunodeficiency virus (HIV)	OR 3.52, 95% CI 2.51–4.94, some ascribable to therapy	[330]

Human papillomavirus (HPV)	High-risk human papillomavirus (HR-HPV) presence implies an OR of 2.18 for PE.	[331]
Meta-analyses	Incidence of PE 19% with asymptomatic bacteriuria, vs 3% (primigravid) or 6% (multigravid) controls (P<0.005)	[332]
	UTI more than twice as likely in severe preeclampsia than in controls	[333]
	OR of 1.6 for PE if UTI present	[334]
	Increased risk of PE OR 1.57 for UTI, 1.76 for periodontal disease	[40]
	Early application of antibiotics in infection reduced PE by 52%	[37]
	Any overt infection led to an RR of 2 for PE	[42]
	UTI has OR of 3.2 for PE; OR = 4.3 if in third trimester	[335]
	UTI has OR of 1.3 for mild/moderate and 1.8 for severe PE	[336]
	Increased risk of PE with UTI (OR 1.22) or antibiotic prescription (OR 1.28)	[337]
	OR of 6.8 for symptomatic bacteriuria in PE vs controls	[338]
	OR 1.3-1.8 of mild or severe PE if exposed to UTI	[339]
	OR 1.4 for PE following UTI	[340]
	OR 1.3 for PE after UTI	[341]
	Meta-analyses showing associations between PD and PE	[41; 342; 343]
	High frequency of neutropenia and sepsis in preeclamptic mothers	[344]
	OR 2.79, CI 2.01-3.01, P<0.0001 for periodontal disease associating with PE	[345]
	Periodontitis at enrolment (OR = 5.78, 95% CI 2.41–13.89) and within 48 hours of delivery (OR = 20.15, 95% CI 4.55–89.29) is associated with an increased risk of preeclampsia	[346]
	Periodontitis associated with PE: OR 7.48 (CI 2.72–22.42)	[347]
Placental microbiome and PE	Many organisms in 13% of PE placentas vs none in controls (P<0.006)	[348]

<i>Plasmodium falciparum</i> (malaria)	Indications that infection with malaria is associated with PE	[349]
	1.5 RR for PE if malarial	[350]
	Seasonality: 5.4-fold increase in eclampsia during malaria season	[351]
	Pre-eclampsia was significantly associated with malaria infection during pregnancy (P<0.03) and 69.7% of cases of pre-eclampsia with infected placenta might be attributable to malaria infection	[352]

Microbiology of semen

Semen itself is very far from being sterile, even in normal individuals, with infection usually being defined as 10^3 organisms.mL⁻¹ semen [353]. Of course the mere existence of sexually transmitted diseases implies strongly that there is a seminal fluid (or semen) microbiome that can vary substantially between individuals, and that can contribute to infection (e.g. [354-356]), fertility [354] (and see below), and any other aspect of pregnancy [357], or even health in later life [358].

It is logical to start here with the observation that semen is a source of microbes from the fact that there are a great many sexually transmitted infectious diseases for which it is the vehicle. Table 3 summarises some of these.

Table 3. Organisms of well-known sexually transmitted diseases that have been associated with semen

Organism (disease)	Comments	References
<i>Chlamydia trachomatis</i>	Effects on fertility	[359]
	32% prevalence in infertile couples	[360]
Human Immunodeficiency Virus (AIDS)	Many examples of seminal transmission via unprotected sex	[361-366]
<i>Neisseria gonorrhoeae</i> (gonorrhoea)	Gonorrhea actually means 'flow of semen'	[367]
	Survives being frozen in semen used for artificial insemination	[368]
	Many anti-gonococcal antibodies also present	[369]
	Same strains in urine and semen; likely origin in urethra	[370]
<i>Treponema pallidum</i> (syphilis)	Infectivity of semen	[371]
	More than half (twelve out of twenty) of the women classified	[372]

	as proved and probably syphilitic had mild to moderate PE	
	Co-infection of syphilis and HIV in men having sex with men	[373]
	Both syphilis and preeclampsia contribute to stillbirths in sub-Saharan Africa	[374]

Notwithstanding the difficulties of measurement [375], there is, in particular, a considerable literature on fertility [376], since infertile males tend to donate sperm for assay in fertility clinics, and infection is a common cause of infertility (e.g. [353] and Table 4). Note that ‘infertility’ is not always an absolute term: pregnancies result in 27% of cases of treated ‘infertile’ couples followed up after trying to conceive for 2y, and with oligozoospermia as the primary cause of infertility [377]. Most studies involve bacteria (bacteriospermia). Papers on this and other microbial properties of semen beyond STDs include those in Table 4.

Table 4. Some examples of the semen microbiome and reproductive biology

Study	Organisms	References
Complementarity between partners	Many. <i>Garnerella vaginalis</i> in female partners was significantly related to inflammation in male genital tracts	[378]
Fertility	Many microbiological changes as a function of fertility (more microbes correlate with lower fertility)	[353; 357; 377; 379-423]
General microbiology	552 different microbes in 182 samples out of 201 tested, simply plating 10 μ L of semen	[424]
	Microbes in 36/37 samples	[425]
	Review	[426]
	35% of samples had microbes	[427]
IVF	No positive antibiotic effect	[428]
LPS and protection by probiotic lactobacilli	(purified LPS)	[429]
Review	Many microbes	[415; 430; 431]
Semen quality	<i>Ralstonia</i> increased in low-quality sperm	[432]
Viral infection	Ebola virus	[433-436]
		[437]
	HIV	[438-440]
	Zika virus	

We deliberately avoid discussing mechanisms in any real detail here, since our purpose is merely to show that semen is commonly infected with microbes, whose presence might well lead to pre-eclampsia. However, we were very struck by the ability of *E. coli* and other organisms [410; 420; 441] actually to immobilise sperm (e.g. [442-445]). As with amyloidogenic blood clotting [446; 447], bacterial LPS [136] may be a chief culprit [429]. The Gram-positive equivalent, lipoteichoic acid (LTA), is just as potent in the fibrinogen-clotting amyloidogen assay [448], but while Gram-positives can also immobilise sperm [449; 450], the influence of purified LTA on sperm seems not to have been tested.

Another prediction from this analysis is that since infection is a significant cause of both infertility and PE (and it may account for 15% of infertile cases [353; 443]), we might expect to see some correlations between them. Although one might argue that anything seen as imperfect 'background' health or subfecundity might impinge on the incidence of PE, the risk ratio for PE in couples whose infertility had an unknown basis was 5.61 (CI 3.3-9.3) in one study in Aberdeen [451] and 1.29 (CI 1.05–1.60) in another in Norway [452]. Time to pregnancy in couples may be used (in part) as a surrogate for (in)fertility and is associated with a variety of poor pregnancy outcomes [453]; in this case, the risk ratio for PE for TTP exceeding 6 months was 2.47 (CI 1.3-4.69) [454]. Given the prevalence of infection in infertile sperm (Table 4), and the frequency of infertility (10% in the Danish study [453], which defined it as couples taking a year or more to conceive), it seems reasonable to suggest that microbiological testing of semen should be done on a more routine basis. It would also help to light up any relationships between the microbiological properties of sperm and the potentially causal consequence of increased PE risk.

More quantitatively, and importantly intellectually, if infection is seen as a major cause of PE, as we argue here, and it is known that infection is a cause of infertility, then one should suppose that infertility, and infertility caused by infection, should be at least as common, and probably more common than is PE, and this is the case, adding some considerable weight to the argument. Indeed, if PE was much more common than infertility or even infection, it would be much harder to argue that the latter was a major cause of the former. In European countries ~10–15% of couples are afflicted by infertility [353; 453], and in some 60% of cases infection or a male factor is implicated [353]. In some countries, the frequency of male infertility is 13-15% <http://bionumbers.hms.harvard.edu/bionumber.aspx?id=113483&ver=0> or higher [455], and the percentage of females with impaired fecundity has been given as 12.3% <https://www.cdc.gov/nchs/fastats/infertility.htm>. These kinds of numbers would imply that 6-9% of couples experience infection- or male-based infertility, and this exceeds the 3-5% incidence of PE.

In a similar vein, antibiotics, provided they can get through the relevant membranes [456-458], should also have benefits on sperm parameters or fertility if a lack of it is caused by infection, and this has indeed been observed (e.g. [407; 423; 459]).

Roles of the prostate and testes

In the previous review, we focussed on the gut, periodontitis, and the urinary tract of the mother as the main source of organisms that might lead to PE. Here we focus on the male, specifically the prostate and the testes, given the evidence for how common infection is in semen. The main function of the prostate gland is to secrete prostate fluid, one of the components of semen. Thus, although it is unlikely that measurement have regularly been done to assess any relationship between this and any adverse effects of pregnancy, it was of interest to establish whether it too is

likely to harbour microbes. Indeed, such 'male accessory gland infection' is common [460-464]. In some cases, the origin is probably periodontal [465]. Recent studies have implicated microbial pattern-recognition receptors, especially Toll-like receptors (TLRs), as well as inflammatory cytokines and their signalling pathways, in testicular function, implying an important link between infection/inflammation and testicular dysfunction [466]. The testes are a common and important site of infection in the male [467; 468], and even bacterial LPS can cause testitis [469]. Similarly, infection (especially urinary tract infection) is a common cause of prostatitis [470-480]. Finally, prostatitis is also a major cause of infertility [460; 461; 463]. Such data contribute strongly to the recognition that semen is not normally going to be sterile, consistent with the view that it is likely to be a major originating cause of the infections characteristic of PE.

Microbial infections in spontaneous abortions, miscarriages and pre-term birth

Our logic would also imply a role for (potentially male-derived) microbes in miscarriages and spontaneous abortions. A microbial component to these seems well established for both miscarriages [481-483] and spontaneous abortions [484-489]. Of course the ability of *Brucella abortus* to induce abortions in domesticated livestock, especially cattle (and occasionally in humans), is well known [490-492]; indeed, bacteriospermia is inimical to fertilisation success [493], and nowadays it is well controlled in livestock by the use of vaccines [494] or antimicrobials [493]. Indeed, stored semen is so widely used for the artificial insemination of livestock in modern agriculture that the recognition that semen is not sterile has led to the routine use of antibiotics in semen 'extenders' (e.g. [495-498]).

The same general logic is true for infection as a common precursor to pre-term birth (PTB) in the absence of PE, where it is much better established (e.g. [499-533]). It arguably has the same basic origins in semen.

Although recurrent pregnancy loss is usually treated separately from infertility (where the role of infection is reasonably well established) it is possible that in many cases it is, like PE, partly just a worsened form of an immune reaction, with both sharing similar causes (including the microbial infection of semen). There is in fact considerable evidence for this (e.g. [120; 413; 534-548]). Of course it is not unreasonable that poor sperm quality, that may be just sufficient to initiate a pregnancy, may ultimately contribute to its premature termination or other disorders of pregnancy, so this association might really be expected. It does, however, add considerable weight to the view that a more common screening of the male than presently done might be of value [549] in assessing a range of pregnancy disorders besides PE. In particular, it seems that infection affects motility (see above), and that this in turn is well correlated [541] with sperm DNA fragmentation and ultimate loss of reproductive quality.

Amyloids in semen are known to enhance HIV infectivity [550]. According to our own recent experimental analyses, they may be caused by bacterial lipopolysaccharide (LPS) [446; 447] or lipoteichoic acid [448]. We note too that the sperm metabolome also influences offspring, e.g. from obese parents [551], and that many other variables are related to sperm quality, including oxidative stress [552-559]. Thus it is entirely reasonable to see semen as a cause of problems as well as benefits to an ensuing pregnancy.

Microbial effects on immunotolerance

If our thesis is sound, one may expect to find evidence for the effects of microbes on the loss of immunotolerance in other settings. One such is tolerance to dietary antigens, of which gluten, a cause of coeliac disease, is pre-eminent. Recently, evidence has come forward that shows a

substantial effect of a reovirus in lowering the immunotolerance to gluten in a mouse model of coeliac disease, and thereby causing inflammation [560; 561]. Interestingly, pregnancies in women with coeliac disease were considerably more susceptible to pre-term birth and other complications than were controls [562-569], especially when mothers were not on a gluten-free diet. Similarly, pre-eclamptic pregnancies led to a much (4-fold) higher likelihood of allergic sensitisation in the offspring [570]. The roles of hygiene, the microbiome and disease are a matter of considerable current interest (e.g. [571]).

It was consequently logical to see if intolerance to peanut antigen was also predictive of PE, but we could find no evidence for this. Again, however, in a study [572] in which PE had roughly its normal prevalence, mothers experiencing it were significantly more likely to give birth to children with increased risk of asthma, eczema, and aeroallergen and food allergy.

Effects of vaccination on pregnancy outcomes, including pre-eclampsia

We noted above (and again below) that the evidence for a role of microbes in pre-term birth (PTB) is overwhelming (also reviewed in [32]). From an immunological point of view, there seems to be a hugely beneficial outcome of vaccination against influenza in terms of lowering pre-term birth [573-578] (cf. [579]) or stillbirth [580]. (PE was not studied, save in [581] where the risk ratio of vaccination (0.484, CI 0.18–1.34) implied a marginal benefit. There do not seem to be any safety issues, either for influenza vaccine [580-601] or for other vaccines [593] such as those against pertussis [602-604] or HPV [605].

As well as miscarriage and pre-term birth, other adverse pregnancy outcomes studied in relation to vaccine exposure [606] include intrauterine growth restriction (IUGR). IUGR frequently presents as the fetal phenotype of pre-eclampsia, sharing a common aetiology in terms of poor placentation in early pregnancy [607]. These other adverse events have been scored more frequently than has been PE, and Table 5 summarises the evidence for a protective effect of vaccines, though it is recognised that there is the potential for considerable confounding effects (e.g. [600; 608]).

Table 5. Protective events of vaccines against various adverse pregnancy outcomes

Adverse event	Risk or Odds ratio (95% Confidence interval) of vaccinated: unvaccinated	Reference
<i>Pre-term birth</i>	[OR = 0.39 (0.18-0.83)]	[574]
	0.56 (0.45-0.70)	[576]
	0.60 0.38–0.94 0.28 (0.11–0.74) during epidemic	[573]
	0.63 (0.47–0.84)	[575]
IUGR	0.15 (0.02-0.94)	[574]
	0.36 (0.17–0.78)	[592]
	0.31 (0.13–0.75)	[573]
	0.63 (0.4–1.0)	[609]

Stillbirth	0.73 (0.55-0.96)	[580]

There are no apparent benefits of vaccine-based immunisation vs recurrent miscarriage [610; 611].

Unrelated to the present question, but very interesting, is the fact that the risk of RA for men was higher among men who fathered their first child at a young age (p for trend <0.001) [612]. This is consistent with the fact that its prevalence in females is 3.5 times higher, and that it has a microbial origin [613-616].

General or specific?

The fact that vaccination against organisms not usually associated with adverse pregnancy outcomes is protective can be interpreted in one (or both) of two ways, i.e. that the vaccine is unselective in terms of inhibiting the effects of its target organism, or the generally raised level of <some kind of> immune response is itself protective. Data to discriminate these are not yet to hand.

In a similar vein, the survival of the host in any 'battle' between host and parasite (e.g. microbe) can be effected in one or both of two main ways: (i) the host invokes antimicrobial processes such as the immune systems described above, or produces antimicrobial compounds, or (ii) the host modifies itself in ways that allow it to become tolerant to the presence of a certain standing crop of microbes. We consider each in turn.

Antimicrobial components of human semen, a part of resistance in the semen microbiome

Antimicrobial peptides (AMPs) (<http://aps.unmc.edu/AP/main.php> [617]) are a well-known part of the defence systems of many animals (e.g. [618-627]) (and indeed plants [618; 628]), and are widely touted as potential anti-infectives (e.g. [629-631]). Their presence in the cells and tissues of the uterus, fetus and the neonate indicates an important role in immunity during pregnancy and in early life [625; 632-636]. Unsurprisingly, they have been proposed as agents for use in preventing the transmission of STDs [637; 638], and as antimicrobials for addition to stored semen for use in agriculture [639-643]. Our interest here, however, is around whether there are natural AMPs in human (or animal) semen, and the answer is in the affirmative. They include SLPI [627], SEVI [644], and in particular the semenogelins [645; 646]. HE2 is another antimicrobial peptide that resides in the epididymis [647; 648], while the human cathelicidin hCAP-18 is inactive in seminal plasma but is processed to the antimicrobial peptide LL-37 by the prostate-derived protease gastricsin [636; 649]. Thus it is clear that at least some of the reason that the semen microbiome is not completely unchecked is down to antimicrobial peptides. Stimulating their production, provided they are not also spermicidal, would seem like an excellent therapeutic option.

Host tolerance to microbial pathogens

It is a commonplace that – for any number of systems biology reasons based on biochemical individuality [650] – even highly virulent diseases do not kill everyone who is exposed to them at the same level. As indicated above, this could be because the host is resistant and simply clears the infections; this is certainly the more traditional view. However, an additional or alternative contribution is because while host do not clear all of them they can develop 'tolerance' to them. This latter view is gaining considerable ground, not least since the work of Schneider, Ayres and colleagues [651] showing that a variety of *Drosophila* mutants with known genetic defects could differentially tolerate infection by *Listeria monocytogenes*. This concept of tolerance [652-659] is very important to our considerations here, since it means that we do indeed have well-established

methods of putting up with microbes more generally, without killing them. It is consistent with clearly established evolutionary theory [660-662], and the relative importance of resistance and tolerance within a population affects host-microbe coevolution [663]. The concept of tolerance sits easily with the Matzinger model of danger/damage (e.g. [155; 157; 158; 160]), as well as the concept of a resident population of dormant microbes [33; 35; 36], and may indeed be seen in terms of a coevolution or mutualistic association [664; 665]. Some specific mechanisms are becoming established, e.g. the variation by microbes of their danger signal to promote host defence [666]. Others, such as the difference in the host metabolomes (that we reviewed [32]) as induced by resistance vs tolerance responses [658] may allow one to infer the relative importance of each. At all events, it is clear from the concept of dormancy that we do not kill all the intracellular microbes that our bodies harbour, and that almost by definition we must then tolerate them. As well as the established maternal immunotolerance of pregnancy, tolerance of microbes seems to be another hallmark of pregnancy.

Sequelae of a role of infection in PE: microbes, molecules and processes

The chief line taken in our previous review [32] and herein is that this should be detectable by various means. Those three chief means involve detecting the microbes themselves, detecting molecules whose concentration changes as a result of the microbes (and their inflammatory components) being present, and detecting host processes whose activities have been changed by the presence of the microbes.

Previously [32], updated here (Table 2), we provided considerable evidence for the presence of microbes within the mother as part of PE. Here we have adduced the equally considerable evidence that in many cases semen is very far from being sterile, and that the source of the originating infection may actually be the father. Equally, we showed [32] that a long list of proteins that were raised (or less commonly lowered) in PE were equally changed by known infections, consistent with the view that PE also involved such infections, albeit at a lower level at which their overt presence could be kept in check. One protein we did not discuss was Placental Protein 13 or galectin 1, so we now discuss this briefly.

Placental protein 13 (galectin 1)

Galectins are glycan-binding proteins that regulate innate and adaptive immune responses. Three of the five human cluster galectins are solely expressed in the placenta [667]. One of these, encoded by the *LGALS13* gene [668], is known as galectin-13 or Placental Protein 13 (PP13) [669]. Its β -sheet-rich 'jelly-roll' structure places it strongly as a galectin homologue [670]. It has a MW of ~16kDa (32kDa dimer [671]) and is expressed solely in the placenta [672] (and see <http://www.proteinatlas.org/ENSG00000105198-LGALS13/tissue>). A decreased placental expression of PP13 and its low concentrations in first trimester maternal sera are associated with elevated risk of preeclampsia [667; 673-675], plausibly reflecting poor placentation. By contrast, and consistent with the usual oxidative stress, there is increased trophoblastic shedding of PP13-immunopositive microvesicles in PE, starting in the second trimester, which leads to high maternal blood PP13 concentrations [667; 676]. Certain alleles such as promoter variant 98A-C predispose strongly to PE [677]. (Galectin-1 is also highly overexpressed in PE [678].) However, as with all the other proteomic biomarkers surveyed previously [32], galectins (including galectin-13 [679] <http://amp.pharm.mssm.edu/Harmonizome/gene/LGALS13>) are clear biomarkers of infection [680].

Toll-like receptors (TLRs)

TLRs are among the best known receptors for 'damage-associated molecular patterns' such as LPS from Gram-negatives (TLR 4 [136; 681-683]), lipoteichoic acids (LTAs) from Gram-positives (TLR2 [684-695]) and viral DNA and its mimics (TLR3) [696].

As expected, they are intimately involved in disorders of pregnancy such as PE [165; 696-708]. Indeed the animal model for preeclampsia developed by Faas and colleagues [709] actually involves injecting an ultra-low dose of LPS into pregnant rat on day 14 of gestation. Overall, such data are fully consistent with the view that infection is a significant part of PE. In view of our suggestions surrounding the role of semen infection in PE it would be of interest to know if these markers were also raised in the semen of partners of women who later manifest PE. Sperm cells are well endowed with TLRs [466; 710-712]. However, we can find only one study showing that increased semen expression of TLRs is indeed observed during inflammation and oxidative stress such as occurs during infection and infertility [713]. A more wide-ranging assessment of TLR expression in sperm cells as a function of fertility seems warranted.

Coagulopathies

Although we discussed this in the previous review [32], some further brief rehearsal is warranted, since coagulopathies are such a common feature of PE (references in [32]). Specifically, our finding that very low concentrations of cell wall products can induce amyloid formation during blood clotting [446; 448] has been further extended to recognise the ubiquity of the phenomenon in chronic, inflammatory diseases [447; 448; 616; 714-716]. Often, an extreme example gives strong pointers, and the syndrome with the highest likelihood of developing PE is antiphospholipid syndrome [717-721], which is also caused by infection [722-727] where the coagulopathies are also especially noteworthy [728-732]. Consequently, the recognition of PE as a amyloidogenic coagulopathy [32; 733-735] is significant.

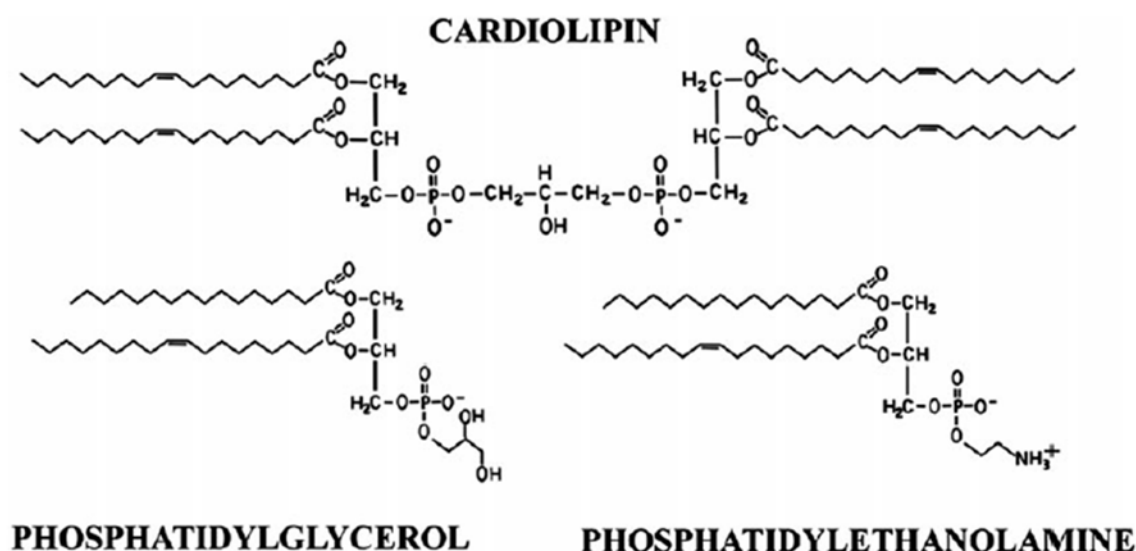
Antiphospholipid syndrome and cardiolipin

Antiphospholipid syndrome (APS) is an autoimmune disorder defined in particular by the presence high circulating titres of what are referred to as antiphospholipid antibodies (aPL) (e.g. [736]). Given that every human cell's plasma membrane contains phospholipids, one might wonder how 'antiphospholipid antibodies' do not simply attack every cell. The answer, most interestingly, is that, despite the name, anticardiolipin antibodies, anti- β 2-glycoprotein-I, and lupus anticoagulant are the main autoantibodies found in antiphospholipid syndrome [737].

In contrast to common phospholipids such as phosphatidylcholine, phosphatidylserine and phosphatidylethanolamine, cardiolipins (1,3-bis(sn-3'-phosphatidyl)-sn-glycerol derivatives) (see Figure 6 for some structures) are synthesised in [738-740] and essentially confined to mitochondria, and in particular the inner mitochondrial membrane, where they serve important functions in oxidative phosphorylation, apoptosis, and heart failure development [740-747]

Overall, there seems to be little doubt that APS and aPL are the result of infection [722; 724-727; 748-750], and that, as with rheumatoid arthritis (see [613-616; 751]), the auto-immune responses

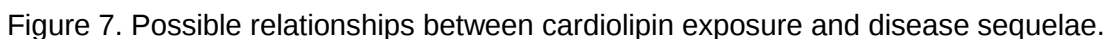
Some phospholipid structures



are essentially due to molecular mimicry.

Figure 6. Some cardiolipin structures.

Now, of course, from an evolutionary point of view, mitochondria are considered to have evolved from (α -Proteo)bacteria [752-758] that were engulfed by a proto-eukaryote [759], and bacteria might consequently be expected to possess cardiolipin. This is very much the case for both Gram-negative and Gram-positive strains [760-764], with Gram-positive organisms typically having the greater content. Particularly significant, from our point of view, is that the relative content of cardiolipin among phospholipids increases enormously as (at least Gram-positive) bacterial cells become dormant [765].



Although often unwritten or implicit, the purposes of much of fundamental biomedical science is to find better diagnostics and treatments for diseases (a combination sometimes referred to as theranostics). Consequently, our purposes here are to rehearse some of those areas where appropriate tests (in the form, ultimately, of randomised clinical trials, RCTs) may be performed. Clearly, as before [32], and recognising the issues of antimicrobial resistance, one avenue would exploit antibiotics much more commonly than now. We note that pharmaceutical drugs are

prescribed or taken during 50% or more of pregnancies [769-778]. Anti-infectives are the most common such drugs, and some 20-25% of women or more are prescribed one or more antibiotics during their pregnancies [770; 771; 774; 776; 777; 779-782].

Given the role of male semen infection, we suggest that more common testing of semen for infection is warranted, especially using molecular tests. Our analyses suggest that antibiotics might also be of benefit to those males presenting with high microbial semen loads or poor fertility [783]. Another strategy might involve stimulating the production of antimicrobial peptides in semen.

Of the list of bacteria given in Table 2 as being associated with PE, *H. pylori* stands out as the most frequent. One may wonder why a vaccine against it has not been developed, but it seems to be less straightforward than for other infections [784; 785], probably because – consistent with its ability to persist within its hosts – it elicits only a poor immune response [786; 787]. Our own experience [788] is that many small molecules can improve the ability of other agents to increase the primary mechanisms that are the target assay, while having no direct effects on them themselves. Although ‘combinatorial’ strategies often lead to quite unexpected beneficial effects (e.g. [789; 790]), this ‘binary weapon’ strategy is both novel and untried.

As also rehearsed in more detail previously (e.g. [791; 792]) many polyphenolic antioxidants act through their ability to chelate unliganded iron, and thereby keep it from doing damage or acting as a source of iron for microbial proliferation. Such molecules may also be expected to be beneficial. Other strategies may be useful for inhibiting the downstream sequelae of latent infections, such as targeting inflammation or coagulopathies.

Conclusions, summary and open questions

We consider that our previous review [32] made a very convincing case for the role of (mostly dormant) microbes in the aetiology of PE. However, we there paid relatively scant attention to two elements, viz (i) the importance of the immune system [145], especially in maternal immunotolerance, and (ii) the idea that possibly the commonest cause of the microbes providing the initial infection was actually infected semen from the father. We also recognise that epigenetic information [358; 793-795] can be provided by the father and this can be hard to discriminate from infection (if not measured), at least in the F₁ generation. This said, microbiological testing of semen seems to be a key discriminator if applied. The ‘danger model’ [155; 157-160], in which it is recognised that immune activation owes more to the detection of specific damage signals than to ‘non-self’, thus seems to be highly relevant to PE [162].

Overall, we think the most important ideas and facts that we have rehearsed here include the following:

- Following Medawar’s recognition of the potential conundrum of paternal alloantigens in pregnancy, most thinking has focused on the role of maternal immunotolerance, and the role of regulatory T cells therein;
- Many examples show that sexual familiarity with the father helps protect against PE; however, this does not explain why in many cases exposure to paternal antigens is actually protective (and not even merely neutral);
- Semen contains many protective and immune-tolerance-inducing substances such as transforming growth factor β (TGF- β);
- However, semen is rarely sterile, and contains many microbes, some of which are not at all benign, and can be transferred to the mother during copulation;

- If one accepts that there is often a microbial component to the development of pre-eclampsia, and we and others have rehearsed the considerable evidence that it is so, then semen seems to a substantial, and previous largely unconsidered source of microbes;
- Some determinands, such as complement factor Bb, seem to reflect microbial infection and not just general inflammation that can have many other causes, and may therefore be of value in untangling the mechanisms involved;
- An improved understanding of the microbiology of semen, and the role of antibiotics and vaccination in the father, seems particularly worthwhile;
- Coagulopathies are a somewhat under-appreciated accompaniment to PE, and may contribute to its aetiology;
- The 'danger model' of immune response seems much better suited to describing events in pregnancy and PE than is the classical self/non-self analysis;
- The features of PE are not at all well recapitulated in animal models [24], and certainly not in rodents. However, it seems likely that they still have much to contribute [796; 797].

Open questions and further research agenda items include the following:

- There is a need for improved molecular and culture-based methods of detecting microbes in blood and tissues in which they are normally considered to be absent, both in the mother and the father;
- Notwithstanding the promise of metabolomics (see e.g. [798; 799]), there remains a need for better diagnostics, especially early in pregnancy;
- Issues of antimicrobial resistance are well known (e.g. [800-802]), and most antibiotics work only on growing cells, so there is a significant role for those that work on persisters and other non-replicating forms [803-805];
- The increasing online availability of patient information will permit greater exploitation to assess these ideas from an epidemiological point of view;

Acknowledgements. DBK thanks the Biotechnology and Biological Sciences Research Council (grant BB/L025752/1) for financial support. LCK is a Science Foundation Ireland Principal Investigator (grant number 08/IN.1/B2083). LCK is also the Director of the Science Foundation Ireland-funded INFANT Research Centre (grant no. 12/RC/2272).

Legends to Figures

Figure 1. A 'mind map' [60] of the review. Start at 'midnight' and read clockwise.

Figure 2. Effective suppression of response to fetal cell trafficking leads to a normal pregnancy, while its failure can lead to pre-eclampsia

Figure 3. Matzinger's 'danger model' vs the classical theory of self vs self-nonself. Based on and redrawn from [158].

Figure 4. The complement system (based on figures in [135; 188]).

Figure 5. Some epidemiological risk factors for pre-eclampsia

Figure 6. Some cardiolipin structures.

Figure 7. Possible relationships between cardiolipin exposure and disease sequelae.

References

- [1] Jeffcoate, T. N. A. (1966). Pre-eclampsia and eclampsia: the disease of theories. *Proc R Soc Med* **59**, 397-404.
- [2] Barad, D. H., Kushnir, V. A. & Gleicher, N. (2017). Focus on recurrent miscarriage phenotypes. *Fertil Steril* **107**, 64-65.
- [3] Grill, S., Rusterholz, C., Zanetti-Dällenbach, R., Tercanli, S., Holzgreve, W., Hahn, S. & Lapaire, O. (2009). Potential markers of preeclampsia--a review. *Reprod Biol Endocrinol* **7**, 70.
- [4] Steegers, E. A. P., von Dadelszen, P., Duvekot, J. J. & Pijnenborg, R. (2010). Pre-eclampsia. *Lancet* **376**, 631-44.
- [5] North, R. A., McCowan, L. M., Dekker, G. A., Poston, L., Chan, E. H., Stewart, A. W., Black, M. A., Taylor, R. S., Walker, J. J., Baker, P. N. & Kenny, L. C. (2011). Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. *BMJ* **342**, d1875.
- [6] Uzan, J., Carbonnel, M., Piconne, O., Asmar, R. & Ayoubi, J. M. (2011). Pre-eclampsia: pathophysiology, diagnosis, and management. *Vasc Health Risk Manag* **7**, 467-74.
- [7] Kenny, L. (2012). Improving diagnosis and clinical management of pre-eclampsia. *MLO Med Lab Obs* **44**, 12, 14.
- [8] Desai, P. (2013). *Obstetric vasculopathies*. Jaypee, New Delhi.
- [9] Chaiworapongsa, T., Chaemsathong, P., Yeo, L. & Romero, R. (2014). Pre-eclampsia part 1: current understanding of its pathophysiology. *Nat Rev Nephrol* **10**, 466-80.
- [10] Kenny, L. C., Black, M. A., Poston, L., Taylor, R., Myers, J. E., Baker, P. N., McCowan, L. M., Simpson, N. A. B., Dekker, G. A., Roberts, C. T., Rodems, K., Noland, B., Raymundo, M., Walker, J. J. & North, R. A. (2014). Early pregnancy prediction of preeclampsia in nulliparous women, combining clinical risk and biomarkers: the Screening for Pregnancy Endpoints (SCOPE) international cohort study. *Hypertension* **64**, 644-52.
- [11] Sircar, M., Thadhani, R. & Karumanchi, S. A. (2015). Pathogenesis of preeclampsia. *Curr Opin Nephrol Hypertens* **24**, 131-8.
- [12] Abalos, E., Cuesta, C., Grosso, A. L., Chou, D. & Say, L. (2013). Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol* **170**, 1-7.
- [13] Vest, A. R. & Cho, L. S. (2014). Hypertension in pregnancy. *Curr Atheroscler Rep* **16**, 395.
- [14] Khan, K. S., Wojdyla, D., Say, L., Gulmezoglu, A. M. & Van Look, P. F. (2006). WHO analysis of causes of maternal death: a systematic review. *Lancet* **367**, 1066-74.
- [15] Duley, L. (2009). The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* **33**, 130-7.
- [16] Cantwell, R., Clutton-Brock, T., Cooper, G., Dawson, A., Drife, J., Garrod, D., Harper, A., Hulbert, D., Lucas, S., McClure, J., Millward-Sadler, H., Neilson, J., Nelson-Piercy, C., Norman, J., O'Herlihy, C., Oates, M., Shakespeare, J., de Swiet, M., Williamson, C., Beale, V., Knight, M., Lennox, C., Miller, A., Parmar, D., Rogers, J. & Springett, A. (2011). Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* **118 Suppl 1**, 1-203.
- [17] Abalos, E., Cuesta, C., Carroli, G., Qureshi, Z., Widmer, M., Vogel, J. P., Souza, J. P. & W. H. O. Multicountry Survey on Maternal Newborn Health Research Network. (2014). 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.
- [18] Ghulmiyyah, L. & Sibai, B. (2012). Maternal mortality from preeclampsia/eclampsia. *Semin Perinatol* **36**, 56-9.
- [19] Brew, O., Sullivan, M. H. & Woodman, A. (2016). Comparison of Normal and Pre-Eclamptic Placental Gene Expression: A Systematic Review with Meta-Analysis. *PLoS One* **11**, e0161504.

- [20] Leavey, K., Benton, S. J., Grynspan, D., Kingdom, J. C., Bainbridge, S. A. & Cox, B. J. (2016). Unsupervised Placental Gene Expression Profiling Identifies Clinically Relevant Subclasses of Human Preeclampsia. *Hypertension* **68**, 137-47.
- [21] Redman, C. W. G. (1991). Current topic: pre-eclampsia and the placenta. *Placenta* **12**, 301-8.
- [22] Roberts, J. M. & Hubel, C. A. (2009). The two stage model of preeclampsia: variations on the theme. *Placenta* **30 Suppl A**, S32-7.
- [23] Baker, P. N. & Kenny, L. C. (2011). *Obstetrics by ten teachers*. CRC Press, Boca Raton, FL.
- [24] Pennington, K. A., Schlitt, J. M., Jackson, D. L., Schulz, L. C. & Schust, D. J. (2012). Preeclampsia: multiple approaches for a multifactorial disease. *Dis Model Mech* **5**, 9-18.
- [25] Redman, C. W. G. (2014). The six stages of pre-eclampsia. *Pregnancy Hypertens* **4**, 246.
- [26] Redman, C. W., Sargent, I. L. & Staff, A. C. (2014). IFPA Senior Award Lecture: making sense of pre-eclampsia - two placental causes of preeclampsia? *Placenta* **35 Suppl**, S20-5.
- [27] Perucci, L. O., Corrêa, M. D., Dusse, L. M., Gomes, K. B. & Sousa, L. P. (2017). Resolution of inflammation pathways in preeclampsia-a narrative review. *Immunol Res* **65**, 774-789.
- [28] Sánchez-Aranguren, L. C., Prada, C. E., Riaño-Medina, C. E. & Lopez, M. (2014). Endothelial dysfunction and preeclampsia: role of oxidative stress. *Front Physiol* **5**, 1.
- [29] Broughton Pipkin, F. & Rubin, P. C. (1994). Pre-eclampsia--the 'disease of theories'. *Br Med Bull* **50**, 381-96.
- [30] Schlembach, D. (2003). Pre-eclampsia--still a disease of theories. *Fukushima J Med Sci* **49**, 69-115.
- [31] Hubel, C. A. (1999). Oxidative stress in the pathogenesis of preeclampsia. *Proc Soc Exp Biol Med* **222**, 222-35.
- [32] Kell, D. B. & Kenny, L. C. (2016). A dormant microbial component in the development of pre-eclampsia. *Front Med Obs Gynecol* **3**, 60.
- [33] Kaprelyants, A. S., Gottschal, J. C. & Kell, D. B. (1993). Dormancy in non-sporulating bacteria. *FEMS Microbiol. Rev.* **10**, 271-286.
- [34] Kell, D. B., Kaprelyants, A. S., Weichert, D. H., Harwood, C. L. & Barer, M. R. (1998). Viability and activity in readily culturable bacteria: a review and discussion of the practical issues. *Antonie van Leeuwenhoek* **73**, 169-187.
- [35] Kell, D. B., Potgieter, M. & Pretorius, E. (2015). Individuality, phenotypic differentiation, dormancy and 'persistence' in culturable bacterial systems: commonalities shared by environmental, laboratory, and clinical microbiology. *F1000Research* **4**, 179.
- [36] Potgieter, M., Bester, J., Kell, D. B. & Pretorius, E. (2015). The dormant blood microbiome in chronic, inflammatory diseases. *FEMS Microbiol Rev* **39**, 567-591.
- [37] Herrera, J. A., Chaudhuri, G. & López-Jaramillo, P. (2001). Is infection a major risk factor for preeclampsia? *Med Hypotheses* **57**, 393-7.
- [38] Trostad, L. I. S., Eskild, A., Bruu, A. L., Jeansson, S. & Jenum, P. A. (2001). Is preeclampsia an infectious disease? *Acta Obstet Gynecol Scand* **80**, 1036-8.
- [39] Todros, T., Vasario, E. & Cardaropoli, S. (2007). Preeclampsia as an infectious disease. *Exp Rev Obs Gynecol* **2**, 735-741.
- [40] Conde-Agudelo, A., Villar, J. & Lindheimer, M. (2008). Maternal infection and risk of preeclampsia: systematic review and metaanalysis. *Am J Obstet Gynecol* **198**, 7-22.
- [41] López-Jaramillo, P., Herrera, J. A., Arenas-Mantilla, M., Jauregui, I. E. & Mendoza, M. A. (2008). Subclinical infection as a cause of inflammation in preeclampsia. *Am J Ther* **15**, 373-6.
- [42] Rustveld, L. O., Kelsey, S. F. & Sharma, R. (2008). Association between maternal infections and preeclampsia: a systematic review of epidemiologic studies. *Matern Child Health J* **12**, 223-42.
- [43] Di Simone, N., Tersigni, C., Cardaropoli, S., Franceschi, F., Di Nicuolo, F., Castellani, R., Bugli, F., de Waure, C., Cavaliere, A. F., Gasbarrini, A., Sanguinetti, M., Scambia, G. & Todros, T. (2017). *Helicobacter pylori* infection contributes to placental impairment in preeclampsia: basic and clinical evidences. *Helicobacter* **22**.
- [44] Nourollahpour Shiadeh, M., Behboodi Moghadam, Z., Adam, I., Saber, V., Bagheri, M. & Rostami, A. (2017). Human infectious diseases and risk of preeclampsia: an updated review of the literature. *Infection*.

- [45] Kleinrouweler, C. E., van Uiter, M., Moerland, P. D., Ris-Stalpers, C., van der Post, J. A. & Afink, G. B. (2013). Differentially expressed genes in the pre-eclamptic placenta: a systematic review and meta-analysis. *PLoS One* **8**, e68991.
- [46] Ubagai, T., Tansho, S., Ieki, R. & Ono, Y. (2012). Evaluation of TREM1 gene expression in circulating polymorphonuclear leukocytes and its inverse correlation with the severity of pathophysiological conditions in patients with acute bacterial infections. *Jpn J Infect Dis* **65**, 376-82.
- [47] Ubagai, T., Nakano, R., Kikuchi, H. & Ono, Y. (2014). Gene expression analysis of TREM1 and GRK2 in polymorphonuclear leukocytes as the surrogate biomarkers of acute bacterial infections. *Int J Med Sci* **11**, 215-21.
- [48] Chung, M. C., Jorgensen, S. C., Popova, T. G., Tonry, J. H., Bailey, C. L. & Popov, S. G. (2009). Activation of plasminogen activator inhibitor implicates protease InhA in the acute-phase response to *Bacillus anthracis* infection. *J Med Microbiol* **58**, 737-44.
- [49] Fillerova, R., Gallo, J., Radvansky, M., Kraiczova, V., Kudelka, M. & Kriegova, E. (2017). Excellent Diagnostic Characteristics for Ultrafast Gene Profiling of DEFA1-IL1B-LTF in Detection of Prosthetic Joint Infections. *J Clin Microbiol* **55**, 2686-2697.
- [50] Dekker, G. A. & Sibai, B. M. (1998). Etiology and pathogenesis of preeclampsia: current concepts. *Am J Obstet Gynecol* **179**, 1359-75.
- [51] Dekker, G. & Robillard, P. Y. (2007). Pre-eclampsia: Is the immune maladaptation hypothesis still standing? An epidemiological update. *J Reprod Immunol* **76**, 8-16.
- [52] Cudihy, D. & Lee, R. V. (2009). The pathophysiology of pre-eclampsia: current clinical concepts. *J Obstet Gynaecol* **29**, 576-82.
- [53] Hsu, P. & Nanan, R. K. (2014). Innate and adaptive immune interactions at the fetal-maternal interface in healthy human pregnancy and pre-eclampsia. *Front Immunol* **5**, 125.
- [54] James, J. L., Whitley, G. S. & Cartwright, J. E. (2010). Pre-eclampsia: fitting together the placental, immune and cardiovascular pieces. *J Pathol* **221**, 363-78.
- [55] Jianjun, Z., Yali, H., Zhiquan, W., Mingming, Z. & Xia, Z. (2010). Imbalance of T-cell transcription factors contributes to the Th1 type immunity predominant in pre-eclampsia. *Am J Reprod Immunol* **63**, 38-45.
- [56] Moffett, A. & Hiby, S. E. (2007). How Does the maternal immune system contribute to the development of pre-eclampsia? *Placenta* **28 Suppl A**, S51-6.
- [57] Redman, C. W. G. & Sargent, I. L. (2010). Immunology of pre-eclampsia. *Am J Reprod Immunol* **63**, 534-43.
- [58] Sargent, I. L., Borzychowski, A. M. & Redman, C. W. (2006). Immunoregulation in normal pregnancy and pre-eclampsia: an overview. *Reprod Biomed Online* **13**, 680-6.
- [59] Dekker, G. A., Robillard, P. Y. & Hulsey, T. C. (1998). Immune maladaptation in the etiology of preeclampsia: a review of corroborative epidemiologic studies. *Obstet Gynecol Surv* **53**, 377-82.
- [60] Buzan, T. (2002). *How to mind map*. Thorsons, London.
- [61] Medawar, P. B. (1953). Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates. *Symp Soc Exp Biol* **7**, 320-338.
- [62] Billington, W. D. (2003). The immunological problem of pregnancy: 50 years with the hope of progress. A tribute to Peter Medawar. *J Reprod Immunol* **60**, 1-11.
- [63] Trowsdale, J. & Betz, A. G. (2006). Mother's little helpers: mechanisms of maternal-fetal tolerance. *Nat Immunol* **7**, 241-6.
- [64] Munoz-Suano, A., Hamilton, A. B. & Betz, A. G. (2011). Gimme shelter: the immune system during pregnancy. *Immunol Rev* **241**, 20-38.
- [65] Bonney, E. A. (2016). Immune Regulation in Pregnancy: A Matter of Perspective? *Obstet Gynecol Clin North Am* **43**, 679-698.
- [66] Colucci, F., Moffett, A. & Trowsdale, J. (2014). Medawar and the immunological paradox of pregnancy: 60 years on. *Eur J Immunol* **44**, 1883-5.
- [67] Haig, D. (1993). Genetic conflicts in human pregnancy. *Q Rev Biol* **68**, 495-532.
- [68] Robertson, S. A. & Sharkey, D. J. (2001). The role of semen in induction of maternal immune tolerance to pregnancy. *Semin Immunol* **13**, 243-54.
- [69] Clark, G. F. & Schust, D. J. (2013). Manifestations of immune tolerance in the human female reproductive tract. *Front Immunol* **4**, 26.

- [70] Gleicher, N., Kushnir, V. A. & Barad, D. H. (2017). Redirecting reproductive immunology research toward pregnancy as a period of temporary immune tolerance. *J Assist Reprod Genet* **34**, 425-430.
- [71] Moffett, A. & Loke, C. (2006). Immunology of placentation in eutherian mammals. *Nat Rev Immunol* **6**, 584-94.
- [72] Dutta, P. & Burlingham, W. J. (2011). Microchimerism: tolerance vs. sensitization. *Curr Opin Organ Transplant* **16**, 359-65.
- [73] Kinder, J. M., Stelzer, I. A., Arck, P. C. & Way, S. S. (2017). Immunological implications of pregnancy-induced microchimerism. *Nat Rev Immunol* **17**, 483-494.
- [74] Knight, M., Redman, C. W. G., Linton, E. A. & Sargent, I. L. (1998). Shedding of syncytiotrophoblast microvilli into the maternal circulation in pre-eclamptic pregnancies. *Br J Obstet Gynaecol* **105**, 632-40.
- [75] Huppertz, B., Kingdom, J., Caniggia, I., Desoye, G., Black, S., Korr, H. & Kaufmann, P. (2003). Hypoxia favours necrotic versus apoptotic shedding of placental syncytiotrophoblast into the maternal circulation. *Placenta* **24**, 181-90.
- [76] Sargent, I. L., Germain, S. J., Sacks, G. P., Kumar, S. & Redman, C. W. G. (2003). Trophoblast deportation and the maternal inflammatory response in pre-eclampsia. *J Reprod Immunol* **59**, 153-60.
- [77] Gupta, A. K., Hasler, P., Holzgreve, W., Gebhardt, S. & Hahn, S. (2005). Induction of neutrophil extracellular DNA lattices by placental microparticles and IL-8 and their presence in preeclampsia. *Hum Immunol* **66**, 1146-54.
- [78] Goswami, D., Tannetta, D. S., Magee, L. A., Fuchisawa, A., Redman, C. W. G., Sargent, I. L. & von Dadelszen, P. (2006). Excess syncytiotrophoblast microparticle shedding is a feature of early-onset pre-eclampsia, but not normotensive intrauterine growth restriction. *Placenta* **27**, 56-61.
- [79] Reddy, A., Zhong, X. Y., Rusterholz, C., Hahn, S., Holzgreve, W., Redman, C. W. G. & Sargent, I. L. (2008). The effect of labour and placental separation on the shedding of syncytiotrophoblast microparticles, cell-free DNA and mRNA in normal pregnancy and pre-eclampsia. *Placenta* **29**, 942-9.
- [80] Hartley, J. D. R., Ferguson, B. J. & Moffett, A. (2015). The role of shed placental DNA in the systemic inflammatory syndrome of preeclampsia. *Am J Obstet Gynecol* **213**, 268-77.
- [81] Clark, D. A., Chaput, A. & Tutton, D. (1986). Active suppression of host-vs-graft reaction in pregnant mice. VII. Spontaneous abortion of allogeneic CBA/J x DBA/2 fetuses in the uterus of CBA/J mice correlates with deficient non-T suppressor cell activity. *J Immunol* **136**, 1668-75.
- [82] Mellor, A. L., Sivakumar, J., Chandler, P., Smith, K., Molina, H., Mao, D. & Munn, D. H. (2001). Prevention of T cell-driven complement activation and inflammation by tryptophan catabolism during pregnancy. *Nat Immunol* **2**, 64-8.
- [83] Wilczyński, J. R. (2006). Immunological analogy between allograft rejection, recurrent abortion and pre-eclampsia - the same basic mechanism? *Hum Immunol* **67**, 492-511.
- [84] Warning, J. C., McCracken, S. A. & Morris, J. M. (2011). A balancing act: mechanisms by which the fetus avoids rejection by the maternal immune system. *Reproduction* **141**, 715-24.
- [85] Kim, C. J., Romero, R., Chaemsaihong, P. & Kim, J. S. (2015). Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. *Am J Obstet Gynecol* **213**, S53-69.
- [86] Raman, K., Wang, H., Troncone, M. J., Khan, W. I., Pare, G. & Terry, J. (2015). Overlap Chronic Placental Inflammation Is Associated with a Unique Gene Expression Pattern. *PLoS One* **10**, e0133738.
- [87] Hyde, K. J. & Schust, D. J. (2016). Immunologic challenges of human reproduction: an evolving story. *Fertil Steril* **106**, 499-510.
- [88] Zelante, T., Pieraccini, G., Scaringi, L., Aversa, F. & Romani, L. (2016). Learning from other diseases: protection and pathology in chronic fungal infections. *Semin Immunopathol* **38**, 239-48.
- [89] Hench, P. S. (1938). The ameliorating effect of pregnancy on chronic atrophic (infectious rheumatoid) arthritis, fibrositis and intermittent hydrarthrit. *Mayo Clin Proc* **13**, 161-167.
- [90] Glyn, J. (1998). The discovery and early use of cortisone. *J R Soc Med* **91**, 513-7.

- [91] de Man, Y. A., Dolhain, R. J., van de Geijn, F. E., Willemsen, S. P. & Hazes, J. M. (2008). Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum* **59**, 1241-8.
- [92] Muñoz-Valle, J. F., Vazquez-Del Mercado, M., García-Iglesias, T., Orozco-Barocio, G., Bernard-Medina, G., Martínez-Bonilla, G., Bastidas-Ramirez, B. E., Navarro, A. D., Bueno, M., Martinez-Lopez, E., Best-Aguilera, C. R., Kamachi, M. & Armendariz-Borunda, J. (2003). T(H)1/T(H)2 cytokine profile, metalloprotease-9 activity and hormonal status in pregnant rheumatoid arthritis and systemic lupus erythematosus patients. *Clin Exp Immunol* **131**, 377-84.
- [93] Nelson, J. L., Hughes, K. A., Smith, A. G., Nisperos, B. B., Branchaud, A. M. & Hansen, J. A. (1993). Maternal-fetal disparity in HLA class II alloantigens and the pregnancy-induced amelioration of rheumatoid arthritis. *N Engl J Med* **329**, 466-71.
- [94] Chiam, N. P. & Lim, L. L. (2014). Uveitis and gender: the course of uveitis in pregnancy. *J Ophthalmol* **2014**, 401915.
- [95] James, D., Steer, P. L., Weiner, C., Gonik, B., Crowther, C. & Robson, S. (2010). High risk pregnancy. Elsevier/Saunders, Amsterdam.
- [96] Khashan, A. S., Kenny, L. C., Laursen, T. M., Mahmood, U., Mortensen, P. B., Henriksen, T. B. & O'Donoghue, K. (2011). Pregnancy and the Risk of Autoimmune Disease. *Plos One* **6**.
- [97] Hunt, J. S., Petroff, M. G., McIntire, R. H. & Ober, C. (2005). HLA-G and immune tolerance in pregnancy. *FASEB J* **19**, 681-93.
- [98] Hviid, T. V. (2006). HLA-G in human reproduction: aspects of genetics, function and pregnancy complications. *Hum Reprod Update* **12**, 209-32.
- [99] Guleria, I. & Sayegh, M. H. (2007). Maternal acceptance of the fetus: true human tolerance. *J Immunol* **178**, 3345-51.
- [100] Dahl, M., Perin, T. L., Djuricic, S., Rasmussen, M., Ohlsson, J., Buus, S., Lindhard, A. & Hviid, T. V. (2014). Soluble human leukocyte antigen-G in seminal plasma is associated with HLA-G genotype: possible implications for fertility success. *Am J Reprod Immunol* **72**, 89-105.
- [101] Lynge Nilsson, L., Djuricic, S. & Hviid, T. V. F. (2014). Controlling the Immunological Crosstalk during Conception and Pregnancy: HLA-G in Reproduction. *Front Immunol* **5**, 198.
- [102] Martínez-Varea, A., Pellicer, B., Perales-Marin, A. & Pellicer, A. (2014). Relationship between maternal immunological response during pregnancy and onset of preeclampsia. *J Immunol Res* **2014**, 210241.
- [103] Sakaguchi, S., Yamaguchi, T., Nomura, T. & Ono, M. (2008). Regulatory T cells and immune tolerance. *Cell* **133**, 775-87.
- [104] Aluvihare, V. R., Kallikourdis, M. & Betz, A. G. (2004). Regulatory T cells mediate maternal tolerance to the fetus. *Nature Immunology* **5**, 266-271.
- [105] Saito, S. (2010). Th17 cells and regulatory T cells: new light on pathophysiology of preeclampsia. *Immunol Cell Biol* **88**, 615-7.
- [106] Saito, S., Nakashima, A., Shima, T. & Ito, M. (2010). Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. *Am J Reprod Immunol* **63**, 601-10.
- [107] Clark, D. A. & Chaouat, G. (2012). Regulatory T cells and reproduction: how do they do it? *J Reprod Immunol* **96**, 1-7.
- [108] Jiang, T. T., Chaturvedi, V., Ertelt, J. M., Kinder, J. M., Clark, D. R., Valent, A. M., Xin, L. & Way, S. S. (2014). Regulatory T cells: new keys for further unlocking the enigma of fetal tolerance and pregnancy complications. *J Immunol* **192**, 4949-56.
- [109] La Rocca, C., Carbone, F., Longobardi, S. & Matarese, G. (2014). The immunology of pregnancy: Regulatory T cells control maternal immune tolerance toward the fetus. *Immunol Lett* **162**, 41-48.
- [110] Guerin, L. R., Prins, J. R. & Robertson, S. A. (2009). Regulatory T-cells and immune tolerance in pregnancy: a new target for infertility treatment? *Hum Reprod Update* **15**, 517-35.
- [111] Alijotas-Reig, J., Llurba, E. & Gris, J. M. (2014). Potentiating maternal immune tolerance in pregnancy: a new challenging role for regulatory T cells. *Placenta* **35**, 241-8.
- [112] Clark, D. A. (2016). The importance of being a regulatory T cell in pregnancy. *J Reprod Immunol* **116**, 60-9.

- [113] Harmon, A. C., Cornelius, D. C., Amaral, L. M., Faulkner, J. L., Cunningham, M. W., Jr., Wallace, K. & LaMarca, B. (2016). The role of inflammation in the pathology of preeclampsia. *Clin Sci (Lond)* **130**, 409-19.
- [114] LaMarca, B., Cornelius, D. C., Harmon, A. C., Amaral, L. M., Cunningham, M. W., Faulkner, J. L. & Wallace, K. (2016). Identifying immune mechanisms mediating the hypertension during preeclampsia. *Am J Physiol Regul Integr Comp Physiol* **311**, R1-9.
- [115] Nancy, P., Tagliani, E., Tay, C. S., Asp, P., Levy, D. E. & Erlebacher, A. (2012). Chemokine Gene Silencing in Decidual Stromal Cells Limits T Cell Access to the Maternal-Fetal Interface. *Science* **336**, 1317-1321.
- [116] Williams, Z. (2012). Inducing tolerance to pregnancy. *N Engl J Med* **367**, 1159-61.
- [117] Samstein, R. M., Josefowicz, S. Z., Arvey, A., Treuting, P. M. & Rudensky, A. Y. (2012). Extrathymic generation of regulatory T cells in placental mammals mitigates maternal-fetal conflict. *Cell* **150**, 29-38.
- [118] Somerset, D. A., Zheng, Y., Kilby, M. D., Sansom, D. M. & Drayson, M. T. (2004). Normal human pregnancy is associated with an elevation in the immune suppressive CD25+ CD4+ regulatory T-cell subset. *Immunology* **112**, 38-43.
- [119] Schumacher, A. & Zenclussen, A. C. (2014). Effects of heme oxygenase-1 on innate and adaptive immune responses promoting pregnancy success and allograft tolerance. *Front Pharmacol* **5**, 288.
- [120] Carp, H. J. A., Selmi, C. & Shoenfeld, Y. (2012). The autoimmune bases of infertility and pregnancy loss. *J Autoimmun* **38**, J266-74.
- [121] Mittrücker, H.-W. & Kaufmann, S. H. E. (2004). Mini-review: regulatory T cells and infection: suppression revisited. *Eur J Immunol* **34**, 306-12.
- [122] Belkaid, Y. (2007). Regulatory T cells and infection: a dangerous necessity. *Nat Rev Immunol* **7**, 875-88.
- [123] Belkaid, Y. & Tarbell, K. (2009). Regulatory T Cells in the Control of Host-Microorganism Interactions. *Annual Review of Immunology* **27**, 551-589.
- [124] Maizels, R. M. & Smith, K. A. (2011). Regulatory T Cells in Infection. *Advances in Immunology: Regulatory T-Cells, Vol 112* **112**, 73-136.
- [125] Sanchez, A. M. & Yang, Y. (2011). The role of natural regulatory T cells in infection. *Immunol Res* **49**, 124-34.
- [126] Berod, L., Puttur, F., Huehn, J. & Sparwasser, T. (2012). Tregs in infection and vaccinology: heroes or traitors? *Microb Biotechnol* **5**, 260-9.
- [127] Williams, Z., Zepf, D., Longtine, J., Anchan, R., Broadman, B., Missmer, S. A. & Hornstein, M. D. (2009). Foreign fetal cells persist in the maternal circulation. *Fertil Steril* **91**, 2593-5.
- [128] Robertson, S. A., Bromfield, J. J. & Tremellen, K. P. (2003). Seminal 'priming' for protection from pre-eclampsia-a unifying hypothesis. *J Reprod Immunol* **59**, 253-65.
- [129] Getz, G. S. (2005). Thematic review series: the immune system and atherogenesis. Bridging the innate and adaptive immune systems. *J Lipid Res* **46**, 619-22.
- [130] Sarma, J. V. & Ward, P. A. (2011). The complement system. *Cell Tissue Res* **343**, 227-35.
- [131] Kennedy, M. A. (2010). A brief review of the basics of immunology: the innate and adaptive response. *Vet Clin North Am Small Anim Pract* **40**, 369-79.
- [132] Warrington, R., Watson, W., Kim, H. L. & Antonetti, F. R. (2011). An introduction to immunology and immunopathology. *Allergy Asthma Clin Immunol* **7 Suppl 1**, S1.
- [133] Abbas, A. K., Lichtman, A. H. & Pillai, S. (2012). *Basic immunology: functions and disorders of the immune system, 8th ed.* Elsevier, St Louis, MO.
- [134] Abbas, A. K., Lichtman, A. H. & Pillai, S. (2016). *Basic immunology: functions and disorders of the immune system, 5th ed.* Elsevier, St Louis, MO.
- [135] Murphy, K. & Weaver, C. (2016). *Janeway's Immunobiology* Garland Science, New York.
- [136] Kell, D. B. & Pretorius, E. (2015). On the translocation of bacteria and their lipopolysaccharides between blood and peripheral locations in chronic, inflammatory diseases: the central roles of LPS and LPS-induced cell death *Integr Biol* **7**, 1339-1377.
- [137] Legutki, J. B., Magee, D. M., Stafford, P. & Johnston, S. A. (2010). A general method for characterization of humoral immunity induced by a vaccine or infection. *Vaccine* **28**, 4529-37.

- [138] Stafford, P., Halperin, R., Legutki, J. B., Magee, D. M., Galgiani, J. & Johnston, S. A. (2012). Physical characterization of the "immunosignaturing effect". *Mol Cell Proteomics* **11**, M111011593.
- [139] Sykes, K. F., Legutki, J. B. & Stafford, P. (2013). Immunosignaturing: a critical review. *Trends biotechnol* **31**, 45-51.
- [140] King, A. E., Kelly, R. W., Sallenave, J.-M., Bocking, A. D. & Challis, J. R. G. (2007). Innate immune defences in the human uterus during pregnancy. *Placenta* **28**, 1099-106.
- [141] Schminkey, D. L. & Groer, M. (2014). Imitating a stress response: a new hypothesis about the innate immune system's role in pregnancy. *Med Hypotheses* **82**, 721-9.
- [142] Zhang, J., Dunk, C., Croy, A. B. & Lye, S. J. (2016). To serve and to protect: the role of decidual innate immune cells on human pregnancy. *Cell Tissue Res* **363**, 249-65.
- [143] Laresgoiti-Servitje, E. (2013). A leading role for the immune system in the pathophysiology of preeclampsia. *J Leukoc Biol* **94**, 247-57.
- [144] Perez-Sepulveda, A., Torres, M. J., Khoury, M. & Illanes, S. E. (2014). Innate immune system and preeclampsia. *Frontiers in Immunology* **5**.
- [145] Saito, S., Shiozaki, A., Nakashima, A., Sakai, M. & Sasaki, Y. (2007). The role of the immune system in preeclampsia. *Mol Aspects Med* **28**, 192-209.
- [146] Brewster, J. A., Orsi, N. M., Gopichandran, N., McShane, P., Ekbote, U. V. & Walker, J. J. (2008). Gestational effects on host inflammatory response in normal and pre-eclamptic pregnancies. *Eur J Obstet Gynecol Reprod Biol* **140**, 21-6.
- [147] Staff, A. C., Johnsen, G. M., Dechend, R. & Redman, C. W. G. (2014). Preeclampsia and uteroplacental acute atherosclerosis: immune and inflammatory factors. *J Reprod Immunol* **101-102**, 120-6.
- [148] Visser, N., van Rijn, B. B., Rijkers, G. T., Franx, A. & Bruinse, H. W. (2007). Inflammatory changes in preeclampsia: current understanding of the maternal innate and adaptive immune response. *Obstet Gynecol Surv* **62**, 191-201.
- [149] Redman, C. W. (1992). Immunological aspects of pre-eclampsia. *Baillieres Clin Obstet Gynaecol* **6**, 601-15.
- [150] Redman, C. W. G., Sargent, I. L. & Taylor, R. N. (2015). Immunology of Normal Pregnancy and Preeclampsia. *Chesley's Hypertensive Disorders in Pregnancy, 4th Edition*, 161-179.
- [151] Parker, L. C., Prince, L. R. & Sabroe, I. (2007). Translational mini-review series on Toll-like receptors: networks regulated by Toll-like receptors mediate innate and adaptive immunity. *Clin Exp Immunol* **147**, 199-207.
- [152] Trinchieri, G. & Sher, A. (2007). Cooperation of Toll-like receptor signals in innate immune defence. *Nat Rev Immunol* **7**, 179-90.
- [153] Nelson, D. E., Ihekweba, A. E. C., Elliott, M., Gibney, C. A., Foreman, B. E., Nelson, G., See, V., Horton, C. A., Spiller, D. G., Edwards, S. W., McDowell, H. P., Unitt, J. F., Sullivan, E., Grimley, R., Benson, N., Broomhead, D. S., Kell, D. B. & White, M. R. H. (2004). Oscillations in NF- κ B signalling control the dynamics of gene expression. *Science* **306**, 704-708.
- [154] Ashall, L., Horton, C. A., Nelson, D. E., Paszek, P., Ryan, S., Sillitoe, K., Harper, C. V., Spiller, D. G., Unitt, J. F., Broomhead, D. S., Kell, D. B., Rand, D., Sée, V. & White, M. R. H. (2009). Pulsatile stimulation determines timing and specificity of NF κ B-dependent transcription. *Science* **324**, 242-246.
- [155] Matzinger, P. (1994). Tolerance, danger, and the extended family. *Annu Rev Immunol* **12**, 991-1045.
- [156] Anderson, C. C. & Matzinger, P. (2000). Danger: the view from the bottom of the cliff. *Semin Immunol* **12**, 231-8; discussion 257-344.
- [157] Matzinger, P. (2001). Essay 1: the Danger model in its historical context. *Scand J Immunol* **54**, 4-9.
- [158] Matzinger, P. (2002). The danger model: a renewed sense of self. *Science* **296**, 301-5.
- [159] Matzinger, P. & Kamala, T. (2011). Tissue-based class control: the other side of tolerance. *Nat Rev Immunol* **11**, 221-30.
- [160] Matzinger, P. (2012). The evolution of the danger theory. *Expert Rev Clin Immunol* **8**, 311-7.
- [161] McCarthy, C. M. & Kenny, L. C. (2016). Immunostimulatory role of mitochondrial DAMPs: alarming for pre-eclampsia? *Am J Reprod Immunol* **76**, 341-347.

- [162] Bonney, E. A. (2007). Preeclampsia: a view through the danger model. *Journal of Reproductive Immunology* **76**, 68-74.
- [163] Sacks, G. P., Studena, K., Sargent, K. & Redman, C. W. G. (1998). Normal pregnancy and preeclampsia both produce inflammatory changes in peripheral blood leukocytes akin to those of sepsis. *Am J Obstet Gynecol* **179**, 80-6.
- [164] Redman, C. W. G., Sacks, G. P. & Sargent, I. L. (1999). Preeclampsia: an excessive maternal inflammatory response to pregnancy. *Am J Obstet Gynecol* **180**, 499-506.
- [165] Kim, Y. M., Romero, R., Oh, S. Y., Kim, C. J., Kilburn, B. A., Armant, D. R., Nien, J. K., Gomez, R., Mazor, M., Saito, S., Abrahams, V. M. & Mor, G. (2005). Toll-like receptor 4: A potential link between "danger signals," the innate immune system and preeclampsia? *Am J Obstet Gynecol* **193**, 921-927.
- [166] Wang, C. C., Yim, K. W., Poon, T. C. W., Choy, K. W., Chu, C. Y., Lui, W. T., Lau, T. K., Rogers, M. S. & Leung, T. N. (2007). Innate immune response by ficolin binding in apoptotic placenta is associated with the clinical syndrome of preeclampsia. *Clin Chem* **53**, 42-52.
- [167] Yeh, C. C., Chao, K. C. & Huang, S. J. (2013). Innate Immunity, Decidual Cells, and Preeclampsia. *Reprod Sci* **20**, 339-353.
- [168] Bounds, K. R., Newell-Rogers, M. K. & Mitchell, B. M. (2015). Four Pathways Involving Innate Immunity in the Pathogenesis of Preeclampsia. *Front Cardiovasc Med* **2**, 20.
- [169] Triggianese, P., Perricone, C., Chimenti, M. S., De Carolis, C. & Perricone, R. (2016). Innate Immune System at the Maternal-Fetal Interface: Mechanisms of Disease and Targets of Therapy in Pregnancy Syndromes. *Am J Reprod Immunol* **76**, 245-57.
- [170] Redman, C. W. G. & Sargent, I. L. (2003). Pre-eclampsia, the placenta and the maternal systemic inflammatory response--a review. *Placenta* **24 Suppl A**, S21-7.
- [171] Hubel, C. A. (2006). Dyslipidemia and pre-eclampsia. In *Pre-eclampsia-aetiology and clinical practice*. (ed. M. A. Belfort and F. Lydall), pp. 164–182. Cambridge University Press, Cambridge.
- [172] Shurin, M. R., Lu, L., Kalinski, P., Stewart-Akers, A. M. & Lotze, M. T. (1999). Th1/Th2 balance in cancer, transplantation and pregnancy. *Springer Semin Immunopathol* **21**, 339-59.
- [173] Saito, S. & Sakai, M. (2003). Th1/Th2 balance in preeclampsia. *J Reprod Immunol* **59**, 161-73.
- [174] Chaouat, G. (2007). The Th1/Th2 paradigm: still important in pregnancy? *Semin Immunopathol* **29**, 95-113.
- [175] Short, S. M., Wolfner, M. F. & Lazzaro, B. P. (2012). Female *Drosophila melanogaster* suffer reduced defense against infection due to seminal fluid components. *J Insect Physiol* **58**, 1192-201.
- [176] Short, S. M. & Lazzaro, B. P. (2013). Reproductive status alters transcriptomic response to infection in female *Drosophila melanogaster*. *G3 (Bethesda)* **3**, 827-40.
- [177] Schjenken, J. E. & Robertson, S. A. (2015). Seminal Fluid Signalling in the Female Reproductive Tract: Implications for Reproductive Success and Offspring Health. *Adv Exp Med Biol* **868**, 127-58.
- [178] Pejic-Karapetrovic, B., Gurnani, K., Russell, M. S., Finlay, B. B., Sad, S. & Krishnan, L. (2007). Pregnancy impairs the innate immune resistance to *Salmonella typhimurium* leading to rapid fatal infection. *J Immunol* **179**, 6088-96.
- [179] Sappenfield, E., Jamieson, D. J. & Kourtis, A. P. (2013). Pregnancy and susceptibility to infectious diseases. *Infect Dis Obstet Gynecol* **2013**, 752852.
- [180] Kourtis, A. P., Read, J. S. & Jamieson, D. J. (2014). Pregnancy and infection. *N Engl J Med* **370**, 2211-8.
- [181] Kraus, T. A., Engel, S. M., Sperling, R. S., Kellerman, L., Lo, Y., Wallenstein, S., Escribese, M. M., Garrido, J. L., Singh, T., Loubeau, M. & Moran, T. M. (2012). Characterizing the pregnancy immune phenotype: results of the viral immunity and pregnancy (VIP) study. *J Clin Immunol* **32**, 300-11.
- [182] Pazos, M., Sperling, R. S., Moran, T. M. & Kraus, T. A. (2012). The influence of pregnancy on systemic immunity. *Immunol Res* **54**, 254-61.

- [183] Lynch, A. M., Murphy, J. R., Byers, T., Gibbs, R. S., Neville, M. C., Giclas, P. C., Salmon, J. E. & Holers, V. M. (2008). Alternative complement pathway activation fragment Bb in early pregnancy as a predictor of preeclampsia. *Am J Obstet Gynecol* **198**, 385 e1-9.
- [184] Lynch, A. M., Gibbs, R. S., Murphy, J. R., Byers, T., Neville, M. C., Giclas, P. C., Salmon, J. E., Van Hecke, T. M. & Holers, V. M. (2008). Complement activation fragment Bb in early pregnancy and spontaneous preterm birth. *Am J Obstet Gynecol* **199**, 354 e1-8.
- [185] Lynch, A. M., Murphy, J. R., Gibbs, R. S., Levine, R. J., Giclas, P. C., Salmon, J. E. & Holers, V. M. (2010). The interrelationship of complement-activation fragments and angiogenesis-related factors in early pregnancy and their association with pre-eclampsia. *BJOG* **117**, 456-62.
- [186] Soto, E., Romero, R., Richani, K., Espinoza, J., Chaiworapongsa, T., Nien, J. K., Edwin, S. S., Kim, Y. M., Hong, J. S., Goncalves, L. F., Yeo, L., Mazon, M., Hassan, S. S. & Kusanovic, J. P. (2010). Preeclampsia and pregnancies with small-for-gestational age neonates have different profiles of complement split products. *J Matern Fetal Neonatal Med* **23**, 646-57.
- [187] Girardi, G., Prohaszka, Z., Bulla, R., Tedesco, F. & Scherjon, S. (2011). Complement activation in animal and human pregnancies as a model for immunological recognition. *Mol Immunol* **48**, 1621-30.
- [188] Lynch, A. M., Gibbs, R. S., Murphy, J. R., Giclas, P. C., Salmon, J. E. & Holers, V. M. (2011). Early Elevations of the Complement Activation Fragment C3a and Adverse Pregnancy Outcomes. *Obs Gynecol* **117**, 75-83.
- [189] Qing, X., Redecha, P. B., Burmeister, M. A., Tomlinson, S., D'Agati, V. D., Davisson, R. L. & Salmon, J. E. (2011). Targeted inhibition of complement activation prevents features of preeclampsia in mice. *Kidney Int* **79**, 331-9.
- [190] Buurma, A., Cohen, D., Veraar, K., Schonkeren, D., Claas, F. H., Bruijn, J. A., Bloemenkamp, K. W. & Baelde, H. J. (2012). Preeclampsia is characterized by placental complement dysregulation. *Hypertension* **60**, 1332-7.
- [191] Wang, W., Irani, R. A., Zhang, Y., Ramin, S. M., Blackwell, S. C., Tao, L., Kellems, R. E. & Xia, Y. (2012). Autoantibody-mediated complement C3a receptor activation contributes to the pathogenesis of preeclampsia. *Hypertension* **60**, 712-21.
- [192] Denny, K. J., Coulthard, L. G., Finnell, R. H., Callaway, L. K., Taylor, S. M. & Woodruff, T. M. (2013). Elevated complement factor C5a in maternal and umbilical cord plasma in preeclampsia. *J Reprod Immunol* **97**, 211-6.
- [193] Denny, K. J., Woodruff, T. M., Taylor, S. M. & Callaway, L. K. (2013). Complement in pregnancy: a delicate balance. *Am J Reprod Immunol* **69**, 3-11.
- [194] Banadakoppa, M., Vidaeff, A. C., Yallampalli, U., Ramin, S. M., Belfort, M. A. & Yallampalli, C. (2015). Complement Split Products in Amniotic Fluid in Pregnancies Subsequently Developing Early-Onset Preeclampsia. *Dis Markers* **2015**, 263109.
- [195] He, Y., Xu, B., Song, D., Yu, F., Chen, Q. & Zhao, M. (2016). Expression of the complement system's activation factors in plasma of patients with early/late-onset severe pre-eclampsia. *Am J Reprod Immunol* **76**, 205-11.
- [196] Hoffman, M. C., Rumer, K. K., Kramer, A., Lynch, A. M. & Winn, V. D. (2014). Maternal and fetal alternative complement pathway activation in early severe preeclampsia. *Am J Reprod Immunol* **71**, 55-60.
- [197] He, Y., Xu, B., Song, D., Yu, F., Chen, Q. & Zhao, M. (2016). Correlations between complement system's activation factors and anti-angiogenesis factors in plasma of patients with early/late-onset severe preeclampsia. *Hypertens Pregnancy* **35**, 499-509.
- [198] Wu, W., Yang, H., Feng, Y., Zhang, P., Li, S., Wang, X., Peng, T., Wang, F., Xie, B., Guo, P., Li, M., Wang, Y., Zhao, N., Wang, D., Wang, S. & Zhang, Y. (2016). Polymorphisms in complement genes and risk of preeclampsia in Taiyuan, China. *Inflamm Res* **65**, 837-45.
- [199] Merle, N. S., Church, S. E., Fremeaux-Bacchi, V. & Roumenina, L. T. (2015). Complement System Part I - Molecular Mechanisms of Activation and Regulation. *Front Immunol* **6**, 262.
- [200] Merle, N. S., Noe, R., Halbwachs-Mecarelli, L., Fremeaux-Bacchi, V. & Roumenina, L. T. (2015). Complement System Part II: Role in Immunity. *Front Immunol* **6**, 257.
- [201] Ponnuraj, K., Xu, Y., Macon, K., Moore, D., Volanakis, J. E. & Narayana, S. V. L. (2004). Structural analysis of engineered Bb fragment of complement factor B: insights into the activation mechanism of the alternative pathway C3-convertase. *Mol Cell* **14**, 17-28.

- [202] Rooijackers, S. H. M., Wu, J., Ruyken, M., van Domselaar, R., Planken, K. L., Tzekou, A., Ricklin, D., Lambris, J. D., Janssen, B. J. C., van Strijp, J. A. G. & Gros, P. (2009). Structural and functional implications of the alternative complement pathway C3 convertase stabilized by a staphylococcal inhibitor. *Nat Immunol* **10**, 721-7.
- [203] Vaisbuch, E., Romero, R., Erez, O., Mazaki-Tovi, S., Kusanovic, J. P., Soto, E., Gotsch, F., Dong, Z., Chaiworapongsa, T., Kim, S. K., Mittal, P., Pacora, P., Yeo, L. & Hassan, S. S. (2009). Fragment Bb in amniotic fluid: evidence for complement activation by the alternative pathway in women with intra-amniotic infection/inflammation. *J Matern Fetal Neonatal Med* **22**, 905-16.
- [204] Li, Q., Li, Y. X., Stahl, G. L., Thurman, J. M., He, Y. & Tong, H. H. (2011). Essential role of factor B of the alternative complement pathway in complement activation and opsonophagocytosis during acute pneumococcal otitis media in mice. *Infect Immun* **79**, 2578-85.
- [205] Velickovic, I., Dalloul, M., Wong, K. A., Bakare, O., Schweis, F., Garala, M., Alam, A., Medranda, G., Lekovic, J., Shuaib, W., Tedjasukmana, A., Little, P., Hanono, D., Wijetilaka, R., Weedon, J., Lin, J., Toledano, R. & Zhang, M. (2015). Complement factor B activation in patients with preeclampsia. *J Reprod Immunol* **109**, 94-100.
- [206] Soto, E., Romero, R., Vaisbuch, E., Erez, O., Mazaki-Tovi, S., Kusanovic, J. P., Dong, Z., Chaiworapongsa, T., Yeo, L., Mittal, P. & Hassan, S. S. (2010). Fragment Bb: evidence for activation of the alternative pathway of the complement system in pregnant women with acute pyelonephritis. *J Matern Fetal Neonatal Med* **23**, 1085-90.
- [207] Lynch, A. M., Eckel, R. H., Murphy, J. R., Gibbs, R. S., West, N. A., Giclas, P. C., Salmon, J. E. & Holers, V. M. (2012). Prepregnancy obesity and complement system activation in early pregnancy and the subsequent development of preeclampsia. *Am J Obstet Gynecol* **206**, 428 e1-8.
- [208] Halmos, A., Rigo, J., Jr., Szijarto, J., Fust, G., Prohaszka, Z. & Molvarec, A. (2012). Circulating ficolin-2 and ficolin-3 in normal pregnancy and pre-eclampsia. *Clin Exp Immunol* **169**, 49-56.
- [209] Haeger, M., Bengtson, A., Karlsson, K. & Heideman, M. (1989). Complement activation and anaphylatoxin (C3a and C5a) formation in preeclampsia and by amniotic fluid. *Obstet Gynecol* **73**, 551-6.
- [210] Haeger, M., Unander, M. & Bengtsson, A. (1991). Complement activation in relation to development of preeclampsia. *Obstet Gynecol* **78**, 46-9.
- [211] Ye, Y., Kong, Y. & Zhang, Y. (2016). Complement Split Products C3a/C5a and Receptors: Are They Regulated by Circulating Angiotensin II Type 1 Receptor Autoantibody in Severe Preeclampsia? *Gynecol Obstet Invest* **81**, 28-33.
- [212] Kestlerová, A., Feyereisl, J., Frisová, V., Měchurová, A., Šůla, K., Zima, T., Běláček, J. & Madar, J. (2012). Immunological and biochemical markers in preeclampsia. *J Reprod Immunol* **96**, 90-4.
- [213] Burwick, R. M., Fichorova, R. N., Dawood, H. Y., Yamamoto, H. S. & Feinberg, B. B. (2013). Urinary excretion of C5b-9 in severe preeclampsia: tipping the balance of complement activation in pregnancy. *Hypertension* **62**, 1040-5.
- [214] Singh, J., Ahmed, A. & Girardi, G. (2011). Role of complement component C1q in the onset of preeclampsia in mice. *Hypertension* **58**, 716-24.
- [215] Marti, J. J. & Herrmann, U. (1977). Immunogestosis: a new etiologic concept of "essential" EPH gestosis, with special consideration of the primigravid patient; preliminary report of a clinical study. *Am J Obstet Gynecol* **128**, 489-93.
- [216] Dekker, G. & Sukcharoen, N. (2004). Etiology of preeclampsia: an update. *J Med Assoc Thai* **87 Suppl 3**, S96-103.
- [217] Larsen, M. H., Bzorek, M., Pass, M. B., Larsen, L. G., Nielsen, M. W., Svendsen, S. G., Lindhard, A. & Hviid, T. V. F. (2011). Human leukocyte antigen-G in the male reproductive system and in seminal plasma. *Mol Hum Reprod* **17**, 727-38.
- [218] Hviid, T. V. F. (2015). Human Leukocyte Antigen-G Within the Male Reproductive System: Implications for Reproduction. *Adv Exp Med Biol* **868**, 171-190.
- [219] Anderson, D. J. & Politch, J. A. (2015). Role of Seminal Plasma in Human Female Reproductive Failure: Immunomodulation, Inflammation, and Infections. *Adv Exp Med Biol* **868**, 159-69.

- [220] Milardi, D., Grande, G., Vincenzoni, F., Castagnola, M. & Marana, R. (2013). Proteomics of human seminal plasma: identification of biomarker candidates for fertility and infertility and the evolution of technology. *Mol Reprod Dev* **80**, 350-7.
- [221] Drabovich, A. P., Saraon, P., Jarvi, K. & Diamandis, E. P. (2014). Seminal plasma as a diagnostic fluid for male reproductive system disorders. *Nat Rev Urol* **11**, 278-88.
- [222] Robertson, S. A. (2005). Seminal plasma and male factor signalling in the female reproductive tract. *Cell Tissue Res* **322**, 43-52.
- [223] Robertson, S. A. (2007). Seminal fluid signaling in the female reproductive tract: lessons from rodents and pigs. *J Anim Sci* **85**, E36-44.
- [224] Robertson, S. A. & Sharkey, D. J. (2016). Seminal fluid and fertility in women. *Fertil Steril* **106**, 511-9.
- [225] García-Montalvo, I. A., Mayoral Andrade, G., Perez-Campos Mayoral, L., Pina Canseco, S., Martinez Cruz, R., Martinez-Cruz, M., Zenteno, E., Pérez-Campos Mayoral, E., Velasco Gallegos, I., Hernandez-Huerta, M. T., Matias-Perez, D. & Pérez-Campos, E. (2016). Molecules in seminal plasma related to platelets in preeclampsia. *Med Hypotheses* **93**, 27-9.
- [226] Robertson, S. A., Guerin, L. R., Moldenhauer, L. M. & Hayball, J. D. (2009). Activating T regulatory cells for tolerance in early pregnancy - the contribution of seminal fluid. *J Reprod Immunol* **83**, 109-16.
- [227] Robertson, S. A., Prins, J. R., Sharkey, D. J. & Moldenhauer, L. M. (2013). Seminal fluid and the generation of regulatory T cells for embryo implantation. *Am J Reprod Immunol* **69**, 315-30.
- [228] Shima, T., Inada, K., Nakashima, A., Ushijima, A., Ito, M., Yoshino, O. & Saito, S. (2015). Paternal antigen-specific proliferating regulatory T cells are increased in uterine-draining lymph nodes just before implantation and in pregnant uterus just after implantation by seminal plasma-priming in allogeneic mouse pregnancy. *J Reprod Immunol* **108**, 72-82.
- [229] Saito, S., Shima, T., Nakashima, A., Inada, K. & Yoshino, O. (2016). Role of Paternal Antigen-Specific Treg Cells in Successful Implantation. *Am J Reprod Immunol* **75**, 310-6.
- [230] Okazaki, T., Akiyoshi, T., Kan, M., Mori, M., Teshima, H. & Shimada, M. (2012). Artificial insemination with seminal plasma improves the reproductive performance of frozen-thawed boar epididymal spermatozoa. *J Androl* **33**, 990-998.
- [231] Bromfield, J. J. (2016). A role for seminal plasma in modulating pregnancy outcomes in domestic species. *Reproduction* **152**, R223-R232.
- [232] Duckitt, K. & Harrington, D. (2005). Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *British Medical Journal* **330**, 565-567.
- [233] Bartsch, E., Medcalf, K. E., Park, A. L., Ray, J. G. & High Risk of Pre-eclampsia Identification, G. (2016). Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ* **353**, i1753.
- [234] Bdolah, Y., Elchalal, U., Natanson-Yaron, S., Yechiam, H., Bdolah-Abram, T., Greenfield, C., Goldman-Wohl, D., Milwidsky, A., Rana, S., Karumanchi, S. A., Yagel, S. & Hochner-Celnikier, D. (2014). Relationship between nulliparity and preeclampsia may be explained by altered circulating soluble fms-like tyrosine kinase 1. *Hypertens Pregnancy* **33**, 250-9.
- [235] Tandberg, A., Klungsoyr, K., Romundstad, L. B. & Skjærven, R. (2015). Pre-eclampsia and assisted reproductive technologies: consequences of advanced maternal age, interbirth intervals, new partner and smoking habits. *BJOG* **122**, 915-22.
- [236] Robillard, P. Y., Hulsey, T. C., Perianin, J., Janky, E., Miri, E. H. & Papiernik, E. (1994). Association of Pregnancy-Induced Hypertension with Duration of Sexual Cohabitation before Conception. *Lancet* **344**, 973-975.
- [237] Einarsson, J. I., Santi-Haghpeykar, H. & Gardner, M. O. (2003). Sperm exposure and development of preeclampsia. *American Journal of Obstetrics and Gynecology* **188**, 1241-1243.
- [238] Saito, A. F., Levine, R. J., Klebanoff, M. A., Martz, K. L., Ewell, M. G., Morris, C. D. & Sibai, B. M. (2003). Abortion, changed paternity, and risk of preeclampsia in nulliparous women. *Am J Epidemiol* **157**, 1108-14.
- [239] Klonoff-Cohen, H. S., Savitz, D. A., Cefalo, R. C. & McCann, M. F. (1989). An epidemiologic study of contraception and preeclampsia. *JAMA* **262**, 3143-7.

- [240] Hernández-Valencia, M., Saldaña Quezada, L., Alvarez Muñoz, M. & Valdez Martínez, E. (2000). Barrier family planning methods as risk factor which predisposes to preeclampsia. *Ginecol Obstet Mex* **68**, 333-338.
- [241] Letur-Köenirsch, H., Peigné, M., Ohl, J., Cédric, I., d'Argent, E. M., Scheffler, F., Grzegorzczak-Martin, V. & de Mouzon, J. (2014). Pregnancies issued from egg donation are associated to a higher risk of hypertensive pathologies then control ART pregnancies. Results of a large comparative cohort study. *Hum Reprod* **29**, 68-69.
- [242] Letur, H., Peigné, M., Ohl, J., Cédric-Durnerin, I., Mathieu-D'Argent, E., Scheffler, F., Grzegorzczak-Martin, V. & de Mouzon, J. (2016). Hypertensive pathologies and egg donation pregnancies: Results of a large comparative cohort study. *Fertil Steril* **106**, 284-90.
- [243] Tarlatzi, T. B., Imbert, R., Alvaro Mercadal, B., Demeestere, I., Venetis, C. A., Englert, Y. & Delbaere, A. (2017). Does oocyte donation compared with autologous oocyte IVF pregnancies have a higher risk of preeclampsia? *Reprod Biomed Online* **34**, 11-18.
- [244] Giannubilo, S. R., Landi, B. & Ciavattini, A. (2014). Preeclampsia: what could happen in a subsequent pregnancy? *Obstet Gynecol Surv* **69**, 747-62.
- [245] Koelman, C. A., Coumans, A. B. C., Nijman, H. W., Doxiadis, I. I. N., Dekker, G. A. & Claas, F. H. J. (2000). Correlation between oral sex and a low incidence of preeclampsia: a role for soluble HLA in seminal fluid? *J Reprod Immunol* **46**, 155-66.
- [246] Martin, R. D. (2016). A Biological Function for Oral Sex?, vol. 2017. Psychology today <https://www.psychologytoday.com/blog/how-we-do-it/201602/biological-function-oral-sex>.
- [247] Saftlas, A. F., Olson, D. R., Franks, A. L., Atrash, H. K. & Pokras, R. (1990). Epidemiology of Preeclampsia and Eclampsia in the United-States, 1979-1986. *Am J Obstet Gynecol* **163**, 460-465.
- [248] Zhang, J., Zeisler, J., Hatch, M. C. & Berkowitz, G. (1997). Epidemiology of pregnancy-induced hypertension. *Epidemiol Rev* **19**, 218-32.
- [249] Lamminpää, R., Vehviläinen-Julkunen, K., Gissler, M. & Heinonen, S. (2012). Preeclampsia complicated by advanced maternal age: a registry-based study on primiparous women in Finland 1997-2008. *BMC Pregnancy Childbirth* **12**, 47.
- [250] Ananth, C. V., Keyes, K. M. & Wapner, R. J. (2013). Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. *BMJ* **347**, f6564.
- [251] Carolan, M. (2013). Maternal age $\geq$ 45 years and maternal and perinatal outcomes: A review of the evidence. *Midwifery* **29**, 479-489.
- [252] Need, J. A., Bell, B., Meffin, E. & Jones, W. R. (1983). Pre-eclampsia in pregnancies from donor inseminations. *J Reprod Immunol* **5**, 329-38.
- [253] Smith, G. N., Walker, M., Tessier, J. L. & Millar, K. G. (1997). Increased incidence of preeclampsia in women conceiving by intrauterine insemination with donor versus partner sperm for treatment of primary infertility. *Am J Obs Gynecol* **177**, 455-458.
- [254] Hoy, J., Venn, A., Halliday, J., Kovacs, G. & Waalwyk, K. (1999). Perinatal and obstetric outcomes of donor insemination using cryopreserved semen in Victoria, Australia. *Hum Reprod* **14**, 1760-4.
- [255] Davis, J. A. & Gallup, G. G. (2006). Preeclampsia and other pregnancy complications as an adaptive response to unfamiliar semen. In *Female Infidelity and Paternal Uncertainty: Evolutionary Perspectives on Male Anti-Cuckoldry Tactics* (ed. S. M. Platek and T. K. Shackelford), pp. 191-204. CUPpip, Cambridge.
- [256] Gleicher, N., Boler, L. R., Jr., Norusis, M. & Del Granado, A. (1986). Hypertensive diseases of pregnancy and parity. *Am J Obstet Gynecol* **154**, 1044-9.
- [257] Roberts, J. M. & Redman, C. W. (1993). Pre-eclampsia: more than pregnancy-induced hypertension. *Lancet* **341**, 1447-51.
- [258] Sibai, B., Dekker, G. & Kupferminc, M. (2005). Pre-eclampsia. *Lancet* **365**, 785-799.
- [259] Luo, Z. C., An, N., Xu, H. R., Larante, A., Audibert, F. & Fraser, W. D. (2007). The effects and mechanisms of primiparity on the risk of pre-eclampsia: a systematic review. *Paediatr Perinat Epidemiol* **21 Suppl 1**, 36-45.
- [260] Hernández-Díaz, S., Toh, S. & Cnattingius, S. (2009). Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. *BMJ* **338**, b2255.

- [261] Wu, C. S., Nohr, E. A., Bech, B. H., Vestergaard, M., Catov, J. M. & Olsen, J. (2009). Health of children born to mothers who had preeclampsia: a population-based cohort study. *Am J Obstet Gynecol* **201**, 269 e1-269 e10.
- [262] English, F. A., Kenny, L. C. & McCarthy, F. P. (2015). Risk factors and effective management of preeclampsia. *Integr Blood Press Control* **8**, 7-12.
- [263] Rich-Edwards, J. W., Ness, R. B. & Roberts, J. M. (2015). Epidemiology of Pregnancy-Related Hypertension. *Chesley's Hypertensive Disorders in Pregnancy, 4th Edition*, 37-55.
- [264] Dildy, G. A., 3rd, Belfort, M. A. & Smulian, J. C. (2007). Preeclampsia recurrence and prevention. *Semin Perinatol* **31**, 135-41.
- [265] Conde-Agudelo, A. & Belizán, J. M. (2000). Risk factors for pre-eclampsia in a large cohort of Latin American and Caribbean women. *BJOG* **107**, 75-83.
- [266] Feeney, J. G. & Scott, J. S. (1980). Pre-eclampsia and changed paternity. *Eur J Obstet Gynecol Reprod Biol* **11**, 35-8.
- [267] Chng, P. K. (1982). Occurrence of pre-eclampsia in pregnancies to three husbands. Case report. *Br J Obstet Gynaecol* **89**, 862-3.
- [268] Robillard, P. Y., Hulsey, T. C., Alexander, G. R., Keenan, A., de Caunes, F. & Papiernik, E. (1993). Paternity patterns and risk of preeclampsia in the last pregnancy in multiparae. *J Reprod Immunol* **24**, 1-12.
- [269] Trupin, L. S., Simon, L. P. & Eskenazi, B. (1996). Change in paternity: a risk factor for preeclampsia in multiparas. *Epidemiology* **7**, 240-4.
- [270] Robillard, P. Y., Dekker, G. A. & Hulsey, T. C. (1999). Revisiting the epidemiological standard of preeclampsia: primigravidity or primipaternity? *Eur J Obstet Gynecol Reprod Biol* **84**, 37-41.
- [271] Tubbergen, P., Lachmeijer, A. M. A., Althuisius, S. M., Vlak, M. E. J., van Geijn, H. P. & Dekker, G. A. (1999). Change in paternity: a risk factor for preeclampsia in multiparous women? *Journal of Reproductive Immunology* **45**, 81-88.
- [272] Li, D. K. & Wi, S. (2000). Changing paternity and the risk of preeclampsia/eclampsia in the subsequent pregnancy. *Am J Epidemiol* **151**, 57-62.
- [273] Dekker, G. A. & Robillard, P. Y. (2005). Preeclampsia: a couple's disease with maternal and fetal manifestations. *Curr Pharm Des* **11**, 699-710.
- [274] Deen, M. E., Ruurda, L. G., Wang, J. & Dekker, G. A. (2006). Risk factors for preeclampsia in multiparous women: primipaternity versus the birth interval hypothesis. *J Matern Fetal Neonatal Med* **19**, 79-84.
- [275] Dekker, G., Robillard, P. Y. & Roberts, C. (2011). The etiology of preeclampsia: the role of the father. *J Reprod Immunol* **89**, 126-32.
- [276] Robillard, P. Y., Dekker, G., Chaouat, G., Hulsey, T. C. & Saftlas, A. (2011). Epidemiological studies on primipaternity and immunology in preeclampsia--a statement after twelve years of workshops. *J Reprod Immunol* **89**, 104-17.
- [277] Nagayama, S., Ohkuchi, A., Usui, R., Matsubara, S. & Suzuki, M. (2014). The Role of the Father in the Occurrence of Preeclampsia. *Med J Obs Gynecol* **2**, 1029-1032.
- [278] Trogstad, L. I. S., Eskild, A., Magnus, P., Samuelsen, S. O. & Nesheim, B. I. (2001). Changing paternity and time since last pregnancy; the impact on pre-eclampsia risk. A study of 547 238 women with and without previous pre-eclampsia. *International Journal of Epidemiology* **30**, 1317-1322.
- [279] Lie, R. T., Rasmussen, S., Brunborg, H., Gjessing, H. K., Lie-Nielsen, E. & Irgens, L. M. (1998). Fetal and maternal contributions to risk of pre-eclampsia: population based study. *BMJ* **316**, 1343-7.
- [280] Triche, E. W., Harland, K. K., Field, E. H., Rubenstein, L. M. & Saftlas, A. F. (2014). Maternal-fetal HLA sharing and preeclampsia: variation in effects by seminal fluid exposure in a case-control study of nulliparous women in Iowa. *J Reprod Immunol* **101-102**, 111-9.
- [281] Saftlas, A. F., Rubenstein, L., Prater, K., Harland, K. K., Field, E. & Triche, E. W. (2014). Cumulative exposure to paternal seminal fluid prior to conception and subsequent risk of preeclampsia. *J Reprod Immunol* **101-102**, 104-10.
- [282] Kho, E. M., McCowan, L. M., North, R. A., Roberts, C. T., Chan, E., Black, M. A., Taylor, R. S., Dekker, G. A. & Consortium, S. (2009). Duration of sexual relationship and its effect on preeclampsia and small for gestational age perinatal outcome. *J Reprod Immunol* **82**, 66-73.

- [283] Bellamy, L., Casas, J. P., Hingorani, A. D. & Williams, D. J. (2007). Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* **335**, 974.
- [284] Salha, O., Sharma, V., Dada, T., Nugent, D., Rutherford, A. J., Tomlinson, A. J., Philips, S., Allgar, V. & Walker, J. J. (1999). The influence of donated gametes on the incidence of hypertensive disorders of pregnancy. *Hum Reprod* **14**, 2268-73.
- [285] Gelbaya, T. A. (2010). Short and long-term risks to women who conceive through *in vitro* fertilization. *Hum Fertil (Camb)* **13**, 19-27.
- [286] van der Hoorn, M. L. P., Lashley, E. E. L. O., Bianchi, D. W., Claas, F. H. J., Schonkeren, C. M. C. & Scherjon, S. A. (2010). Clinical and immunologic aspects of egg donation pregnancies: a systematic review. *Hum Reprod Update* **16**, 704-12.
- [287] Masoudian, P., Nasr, A., de Nanassy, J., Fung-Kee-Fung, K., Bainbridge, S. A. & El Demellawy, D. (2016). Oocyte donation pregnancies and the risk of preeclampsia or gestational hypertension: a systematic review and metaanalysis. *Am J Obstet Gynecol* **214**, 328-39.
- [288] Porreco, R. P. & Heyborne, K. D. (2017). Immunogenesis of preeclampsia: lessons from donor gametes. *J Matern Fetal Neonatal Med*, 1-7.
- [289] Dude, A. M., Yeh, J. S. & Muasher, S. J. (2016). Donor oocytes are associated with preterm birth when compared to fresh autologous in vitro fertilization cycles in singleton pregnancies. *Fertil Steril* **106**, 660-5.
- [290] Stoop, D., Baumgarten, M., Haentjens, P., Polyzos, N. P., De Vos, M., Verheyen, G., Camus, M. & Devroey, P. (2012). Obstetric outcome in donor oocyte pregnancies: a matched-pair analysis. *Reprod Biol Endocrinol* **10**, 42.
- [291] Levron, Y., Dviri, M., Segol, I., Yerushalmi, G. M., Hourvitz, A., Orvieto, R., Mazaki-Tovi, S. & Yinon, Y. (2014). The 'immunologic theory' of preeclampsia revisited: a lesson from donor oocyte gestations. *Am J Obstet Gynecol* **211**, 383 e1-5.
- [292] Fox, N. S., Roman, A. S., Saltzman, D. H., Hourizadeh, T., Hastings, J. & Rebarber, A. (2014). Risk factors for preeclampsia in twin pregnancies. *Am J Perinatol* **31**, 163-6.
- [293] Thomopoulos, C., Salamalekis, G., Kintis, K., Andrianopoulou, I., Michalopoulou, H., Skalis, G., Archontakis, S., Argyri, O., Tsioufis, C., Makris, T. K. & Salamalekis, E. (2017). Risk of hypertensive disorders in pregnancy following assisted reproductive technology: overview and meta-analysis. *J Clin Hypertens (Greenwich)* **19**, 173-183.
- [294] Blázquez, A., García, D., Rodríguez, A., Vassena, R., Figueras, F. & Vernaev, V. (2016). Is oocyte donation a risk factor for preeclampsia? A systematic review and meta-analysis. *J Assist Reprod Genet* **33**, 855-63.
- [295] Klatsky, P. C., Delaney, S. S., Caughey, A. B., Tran, N. D., Schattman, G. L. & Rosenwaks, Z. (2010). The role of embryonic origin in preeclampsia: a comparison of autologous in vitro fertilization and ovum donor pregnancies. *Obstet Gynecol* **116**, 1387-92.
- [296] Kroon, B., Hart, R. J., Wong, B. M., Ford, E. & Yazdani, A. (2012). Antibiotics prior to embryo transfer in ART. *Cochrane Database Syst Rev*, CD008995.
- [297] Sibai, B. M., Mercer, B. & Sarinoglu, C. (1991). Severe preeclampsia in the second trimester: recurrence risk and long-term prognosis. *Am J Obstet Gynecol* **165**, 1408-12.
- [298] van Rijn, B. B., Hoeks, L. B., Bots, M. L., Franx, A. & Bruinse, H. W. (2006). Outcomes of subsequent pregnancy after first pregnancy with early-onset preeclampsia. *Am J Obstet Gynecol* **195**, 723-8.
- [299] Mostello, D., Kallogjeri, D., Tungsiripat, R. & Leet, T. (2008). Recurrence of preeclampsia: effects of gestational age at delivery of the first pregnancy, body mass index, paternity, and interval between births. *Am J Obstet Gynecol* **199**, 55 e1-7.
- [300] Rasmussen, S., Irgens, L. M., Albrechtsen, S. & Dalaker, K. (2000). Predicting preeclampsia in the second pregnancy from low birth weight in the first pregnancy. *Obstet Gynecol* **96**, 696-700.
- [301] Thevaranjan, N., Puchta, A., Schulz, C., Naidoo, A., Szamosi, J. C., Verschoor, C. P., Loukov, D., Schenck, L. P., Jury, J., Foley, K. P., Schertzer, J. D., Larche, M. J., Davidson, D. J., Verdu, E. F., Surette, M. G. & Bowdish, D. M. (2017). Age-Associated Microbial Dysbiosis Promotes Intestinal Permeability, Systemic Inflammation, and Macrophage Dysfunction. *Cell Host Microbe* **21**, 455-466 e4.

- [302] Astin, M., Scott, J. R. & Worley, R. J. (1981). Pre-eclampsia/eclampsia: a fatal father factor. *Lancet* **2**, 533.
- [303] Wang, J. X., Knottnerus, A. M., Schuit, G., Norman, R. J., Chan, A. & Dekker, G. A. (2002). Surgically obtained sperm, and risk of gestational hypertension and pre-eclampsia. *Lancet* **359**, 673-4.
- [304] Le Ray, C., Scherier, S., Anselem, O., Marszalek, A., Tsatsaris, V., Cabrol, D. & Goffinet, F. (2012). Association between oocyte donation and maternal and perinatal outcomes in women aged 43 years or older. *Hum Reprod* **27**, 896-901.
- [305] González-Comadran, M., Avila, J. U., Tascón, A. S., Jimenéz, R., Solà, I., Brassesco, M., Carreras, R. & Checa, M. Á. (2014). The impact of donor insemination on the risk of preeclampsia: a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol* **182**, 160-166.
- [306] Thomopoulos, C., Tsioufis, C., Michalopoulou, H., Makris, T., Papademetriou, V. & Stefanadis, C. (2013). Assisted reproductive technology and pregnancy-related hypertensive complications: a systematic review. *J Hum Hypertens* **27**, 148-57.
- [307] Wu, H., Estill, M. S., Alexander Shershebnv, Suvorov, A., Krawetz, S. A., Whitcomb, B. W., Dinnie, H., Rahil, T., Sites, C. K. & Pilsner, J. R. (2017). Preconception urinary phthalate concentrations and sperm DNA methylation profiles among men undergoing IVF treatment: a cross-sectional study. *Hum Reprod*.
- [308] Verstraelen, H. & Senok, A. C. (2005). Vaginal lactobacilli, probiotics, and IVF. *Reprod Biomed Online* **11**, 674-5.
- [309] Reid, G., Brigidi, P., Burton, J. P., Contractor, N., Duncan, S., Fargier, E., Hill, C., Lebeer, S., Martin, R., McBain, A. J., Mor, G., O'Neill, C., Rodriguez, J. M., Swann, J., van Hemert, S. & Ansell, J. (2015). Microbes central to human reproduction. *Am J Reprod Immunol* **73**, 1-11.
- [310] Sirota, I., Zarek, S. M. & Segars, J. H. (2014). Potential influence of the microbiome on infertility and assisted reproductive technology. *Semin Reprod Med* **32**, 35-42.
- [311] Xie, F., Hu, Y., Magee, L. A., Money, D. M., Patrick, D. M., Brunham, R. M., Thomas, E., von Dadelszen, P. & for the Toxaemia group. (2010). *Chlamydia pneumoniae* infection in preeclampsia. *Hypertens Pregnancy* **29**, 468-77.
- [312] Heine, R. P., Ness, R. B. & Roberts, J. M. (2003). Seroprevalence of antibodies to *Chlamydia pneumoniae* in women with preeclampsia. *Obstet Gynecol* **101**, 221-6.
- [313] El-Shourbagy, M. A. A., El-Refaie, T. A., Sayed, K. K. A., Wahba, K. A. H., El-Din, A. S. S. & Fathy, M. M. (2011). Impact of seroconversion and antichlamydial treatment on the rate of pre-eclampsia among Egyptian primigravidae. *Int J Gynaecol Obstet* **113**, 137-40.
- [314] Mosbah, A. & Nabel, Y. (2016). *Helicobacter pylori*, *Chlamydiae pneumoniae* and trachomatis as probable etiological agents of preeclampsia. *J Matern-Fetal Neonat Med* **29**, 1607-1612.
- [315] Gomez, L. M. & Parry, S. (2009). Trophoblast infection with *Chlamydia pneumoniae* and adverse pregnancy outcomes associated with placental dysfunction. *Am J Obstet Gynecol* **200**, 526 e1-7.
- [316] Haggerty, C. L., Klebanoff, M. A., Panum, I., Uldum, S. A., Bass, D. C., Olsen, J., Roberts, J. M. & Ness, R. B. (2013). Prenatal *Chlamydia trachomatis* infection increases the risk of preeclampsia. *Pregnancy Hypertens* **3**, 151-154.
- [317] Haggerty, C. L., Panum, I., Uldum, S. A., Bass, D. C., Olsen, J., Darville, T., Eastman, J. M., Simhan, H. N., Roberts, J. M. & Ness, R. B. (2013). *Chlamydia trachomatis* infection may increase the risk of preeclampsia. *Pregnancy Hypertens* **3**, 28-33.
- [318] Xie, F., Hu, Y., Magee, L. A., Money, D. M., Patrick, D. M., Kraiden, M., Thomas, E., von Dadelszen, P. & Toxemia Study, G. (2010). An association between cytomegalovirus infection and pre-eclampsia: a case-control study and data synthesis. *Acta Obstet Gynecol Scand* **89**, 1162-7.
- [319] Xie, F., von Dadelszen, P. & Nadeau, J. (2014). CMV infection, TLR-2 and -4 expression, and cytokine profiles in early-onset preeclampsia with HELLP syndrome. *Am J Reprod Immunol* **71**, 379-86.
- [320] Ponzetto, A., Cardaropoli, S., Piccoli, E., Rolfo, A., Gennero, L., Kanduc, D. & Todros, T. (2006). Pre-eclampsia is associated with *Helicobacter pylori* seropositivity in Italy. *J Hypertens* **24**, 2445-9.

- [321] Panarelli, M. & Sattar, N. (2006). Pre-eclampsia associated with *Helicobacter pylori* seropositivity. *J Hypertens* **24**, 2353-2354.
- [322] Tersigni, C., Franceschi, F., Todros, T., Cardaropoli, S., Scambia, G. & Di Simone, N. (2014). Insights into the Role of *Helicobacter pylori* Infection in Preeclampsia: From the Bench to the Bedside. *Front Immunol* **5**, 484.
- [323] Üstün, Y., Engin-Üstün, Y., Ozkaplan, E., Otlu, B. & Sait Tekerekoğlu, M. (2010). Association of *Helicobacter pylori* infection with systemic inflammation in preeclampsia. *J Matern Fetal Neonatal Med* **23**, 311-4.
- [324] Aksoy, H., Ozkan, A., Aktas, F. & Borekci, B. (2009). *Helicobacter pylori* seropositivity and its relationship with serum malondialdehyde and lipid profile in preeclampsia. *J Clin Lab Anal* **23**, 219-222.
- [325] Cardaropoli, S., Rolfo, A. & Todros, T. (2014). *Helicobacter pylori* and pregnancy-related disorders. *World J Gastroenterol* **20**, 654-64.
- [326] Pugliese, A., Beltramo, T., Todros, T., Cardaropoli, S. & Ponzetto, A. (2008). Interleukin-18 and gestosis: correlation with *Helicobacter pylori* seropositivity. *Cell Biochem Funct* **26**, 817-9.
- [327] Cardaropoli, S., Giuffrida, D., Piazzese, A. & Todros, T. (2015). *Helicobacter pylori* seropositivity and pregnancy-related diseases: a prospective cohort study. *J Reprod Immunol* **109**, 41-7.
- [328] Cardaropoli, S., Rolfo, A., Piazzese, A., Ponzetto, A. & Todros, T. (2011). *Helicobacter pylori*'s virulence and infection persistence define pre-eclampsia complicated by fetal growth retardation. *World J Gastroenterol* **17**, 5156-65.
- [329] den Hollander, W. J., Schalekamp-Timmermans, S., Holster, I. L., Jaddoe, V. W., Hofman, A., Moll, H. A., Perez-Perez, G. I., Blaser, M. J., Steegers, E. A. P. & Kuipers, E. J. (2017). *Helicobacter pylori* colonization and pregnancies complicated by preeclampsia, spontaneous prematurity, and small for gestational age birth. *Helicobacter* **22**.
- [330] Sansone, M., Sarno, L., Saccone, G., Berghella, V., Maruotti, G. M., Migliucci, A., Capone, A. & Martinelli, P. (2016). Risk of Preeclampsia in Human Immunodeficiency Virus-Infected Pregnant Women. *Obstet Gynecol* **127**, 1027-32.
- [331] McDonnold, M., Dunn, H., Hester, A., Pacheco, L. D., Hankins, G. D., Saade, G. R. & Costantine, M. M. (2014). High risk human papillomavirus at entry to prenatal care and risk of preeclampsia. *Am J Obstet Gynecol* **210**, 138 e1-5.
- [332] Hill, J. A., Devoe, L. D. & Bryans, C. I., Jr. (1986). Frequency of asymptomatic bacteriuria in preeclampsia. *Obstet Gynecol* **67**, 529-32.
- [333] Hsu, C. D. & Witter, F. R. (1995). Urogenital infection in preeclampsia. *Int J Gynaecol Obstet* **49**, 271-5.
- [334] Mittendorf, R., Lain, K. Y., Williams, M. A. & Walker, C. K. (1996). Preeclampsia. A nested, case-control study of risk factors and their interactions. *J Reprod Med* **41**, 491-6.
- [335] Easter, S. R., Cantonwine, D. E., Zera, C. A., Lim, K. H., Parry, S. I. & McElrath, T. F. (2016). Urinary tract infection during pregnancy, angiogenic factor profiles, and risk of preeclampsia. *Am J Obs Gynecol* **214**.
- [336] Mazor-Dray, E., Levy, A., Schlaeffer, F. & Sheiner, E. (2009). Maternal urinary tract infection: is it independently associated with adverse pregnancy outcome? *J Matern Fetal Neonatal Med* **22**, 124-8.
- [337] Minassian, C., Thomas, S. L., Williams, D. J., Campbell, O. & Smeeth, L. (2013). Acute maternal infection and risk of pre-eclampsia: a population-based case-control study. *PLoS One* **8**, e73047.
- [338] Rezavand, N., Veisi, F., Zangane, M., Amini, R. & Almasi, A. (2016). Association between Asymptomatic Bacteriuria and Pre-Eclampsia. *Glob J Health Sci* **8**, 235-239.
- [339] Karmon, A. & Sheiner, E. (2008). The relationship between urinary tract infection during pregnancy and preeclampsia: causal, confounded or spurious? *Arch Gynecol Obstet* **277**, 479-81.
- [340] Villar, J., Carroli, G., Wojdyla, D., Abalos, E., Giordano, D., Ba'ageel, H., Farnot, U., Bergsjø, P., Bakketeig, L., Lumbiganon, P., Campodonico, L., Al-Mazrou, Y., Lindheimer, M., Kramer, M. & World Health Organization Antenatal Care Trial Research Group. (2006). Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? *Am J Obstet Gynecol* **194**, 921-31.

- [341] Bánhidý, F., Ács, N., Puhó, E. H. & Czeizel, A. E. (2007). Pregnancy complications and birth outcomes of pregnant women with urinary tract infections and related drug treatments. *Scand J Infect Dis* **39**, 390-7.
- [342] Ide, M. & Papapanou, P. N. (2013). Epidemiology of association between maternal periodontal disease and adverse pregnancy outcomes--systematic review. *J Periodontol* **84**, S181-94.
- [343] Dunlop, A. L., Mulle, J. G., Ferranti, E. P., Edwards, S., Dunn, A. B. & Corwin, E. J. (2015). Maternal Microbiome and Pregnancy Outcomes That Impact Infant Health: A Review. *Adv Neonatal Care* **15**, 377-85.
- [344] Doron, M. W., Makhlof, R. A., Katz, V. L., Lawson, E. E. & Stiles, A. D. (1994). Increased Incidence of Sepsis at Birth in Neutropenic Infants of Mothers with Preeclampsia. *J Pediatr* **125**, 452-458.
- [345] Wei, B.-J., Chen, Y.-J., Yu, L. & Wu, B. (2013). Periodontal disease and risk of preeclampsia: a meta-analysis of observational studies. *PLoS One* **8**, e70901.
- [346] Shetty, M., Shetty, P. K., Ramesh, A., Thomas, B., Prabhu, S. & Rao, A. (2010). Periodontal disease in pregnancy is a risk factor for preeclampsia. *Acta Obstet Gynecol Scand* **89**, 718-21.
- [347] Kumar, A., Basra, M., Begum, N., Rani, V., Prasad, S., Lamba, A. K., Verma, M., Agarwal, S. & Sharma, S. (2013). Association of maternal periodontal health with adverse pregnancy outcome. *J Obstet Gynaecol Res* **39**, 40-5.
- [348] Amarasekara, R., Jayasekara, R. W., Senanayake, H. & Dissanayake, V. H. W. (2015). Microbiome of the placenta in pre-eclampsia supports the role of bacteria in the multifactorial cause of pre-eclampsia. *J Obstet Gynaecol Res* **41**, 662-669.
- [349] Hlimi, T. (2015). Association of anemia, pre-eclampsia and eclampsia with seasonality: A realist systematic review. *Health & Place* **31**, 180-192.
- [350] Brabin, B. J. & Johnson, P. M. (2005). Placental malaria and pre-eclampsia through the looking glass backwards? *J Reprod Immunol* **65**, 1-15.
- [351] Anya, S. E. (2004). Seasonal variation in the risk and causes of maternal death in the Gambia: malaria appears to be an important factor. *Am J Trop Med Hyg* **70**, 510-3.
- [352] Sartelet, H., Rogier, C., Milko-Sartelet, I., Angel, G. & Michel, G. (1996). Malaria associated pre-eclampsia in Senegal. *Lancet* **347**, 1121.
- [353] Keck, C., Gerber-Schafer, C., Clad, A., Wilhelm, C. & Breckwoldt, M. (1998). Seminal tract infections: impact on male fertility and treatment options. *Hum Reprod Update* **4**, 891-903.
- [354] Ochsendorf, F. R. (2008). Sexually transmitted infections: impact on male fertility. *Andrologia* **40**, 72-5.
- [355] Swidsinski, A., Dörffel, Y., Loening-Baucke, V., Mendling, W., Verstraelen, H., Dieterle, S. & Schilling, J. (2010). Desquamated epithelial cells covered with a polymicrobial biofilm typical for bacterial vaginosis are present in randomly selected cryopreserved donor semen. *FEMS Immunol Med Microbiol* **59**, 399-404.
- [356] Gallo, M. F., Warner, L., King, C. C., Sobel, J. D., Klein, R. S., Cu-Uvin, S., Rompalo, A. M. & Jamieson, D. J. (2011). Association between semen exposure and incident bacterial vaginosis. *Infect Dis Obstet Gynecol* **2011**, 842652.
- [357] Paavonen, J. & Eggert-Kruse, W. (1999). *Chlamydia trachomatis*: impact on human reproduction. *Hum Reprod Update* **5**, 433-47.
- [358] Rando, O. J. & Simmons, R. A. (2015). I'm eating for two: parental dietary effects on offspring metabolism. *Cell* **161**, 93-105.
- [359] Dehghan Marvast, L., Aflatoonian, A., Talebi, A. R., Ghasemzadeh, J. & Pacey, A. A. (2016). Semen inflammatory markers and *Chlamydia trachomatis* infection in male partners of infertile couples. *Andrologia* **48**, 729-36.
- [360] López-Hurtado, M., Velazco-Fernández, M., Pedraza-Sánchez, M. J. E., Flores-Salazar, V. R., Villagrana Zesati, R. & Guerra-Infante, F. M. (2017). Molecular detection of *Chlamydia trachomatis* and semen quality of sexual partners of infertile women. *Andrologia*.
- [361] Delwart, E. L., Mullins, J. I., Gupta, P., Learn, G. H., Jr., Holodniy, M., Katzenstein, D., Walker, B. D. & Singh, M. K. (1998). Human immunodeficiency virus type 1 populations in blood and semen. *J Virol* **72**, 617-23.

- [362] Winter, A. J., Taylor, S., Workman, J., White, D., Ross, J. D., Swan, A. V. & Pillay, D. (1999). Asymptomatic urethritis and detection of HIV-1 RNA in seminal plasma. *Sex Transm Infect* **75**, 261-3.
- [363] Pilcher, C. D., Joaki, G., Hoffman, I. F., Martinson, F. E., Mapanje, C., Stewart, P. W., Powers, K. A., Galvin, S., Chilongozi, D., Gama, S., Price, M. A., Fiscus, S. A. & Cohen, M. S. (2007). Amplified transmission of HIV-1: comparison of HIV-1 concentrations in semen and blood during acute and chronic infection. *AIDS* **21**, 1723-30.
- [364] Hladik, F. & McElrath, M. J. (2008). Setting the stage: host invasion by HIV. *Nat Rev Immunol* **8**, 447-57.
- [365] Liu, C. M., Osborne, B. J. W., Hungate, B. A., Shahabi, K., Huibner, S., Lester, R., Dwan, M. G., Kovacs, C., Contente-Cuomo, T. L., Benko, E., Aziz, M., Price, L. B. & Kaul, R. (2014). The semen microbiome and its relationship with local immunology and viral load in HIV infection. *PloS Path* **10**.
- [366] Rametse, C. L., Olivier, A. J., Masson, L., Barnabas, S., McKinnon, L. R., Ngcapu, S., Liebenberg, L. J., Jaumdally, S. Z., Gray, C. M., Jaspan, H. B. & Passmore, J. A. (2014). Role of semen in altering the balance between inflammation and tolerance in the female genital tract: does it contribute to HIV risk? *Viral Immunol* **27**, 200-6.
- [367] Gruber, F., Lipozencic, J. & Kehler, T. (2015). History of venereal diseases from antiquity to the renaissance. *Acta Dermatovenereol Croat* **23**, 1-11.
- [368] Sherman, J. K. & Rosenfeld, J. (1975). Importance of frozen-stored human semen in the spread of gonorrhea. *Fertil Steril* **26**, 1043-7.
- [369] Zheng, H. (1997). Analysis of the antigen-antibody specificity in the semen of patients with *Neisseria gonorrhoeae*. *Chin Med Sci J* **12**, 47-9.
- [370] Isbey, S. F., Alcorn, T. M., Davis, R. H., Haizlip, J., Leone, P. A. & Cohen, M. S. (1997). Characterisation of *Neisseria gonorrhoeae* in semen during urethral infection in men. *Genitourin Med* **73**, 378-82.
- [371] Kertsész, G. (1931). A new method of inoculation to prove the infectivity of the semen in latent syphilis. *Br J Dermatol Syph* **43**, 588-592.
- [372] Adeoba, A. (1967). Interpretation of positive serological tests for syphilis in pregnancy. *Br J Vener Dis* **43**, 249-58.
- [373] Burchell, A. N., Allen, V. G., Gardner, S. L., Moravan, V., Tan, D. H. S., Grewal, R., Raboud, J., Bayoumi, A. M., Kaul, R., Mazzulli, T., Mcgee, F., Rourke, S. B. & Team, O. C. S. (2015). High incidence of diagnosis with syphilis co-infection among men who have sex with men in an HIV cohort in Ontario, Canada. *BMC Infect Dis* **15**.
- [374] Goldenberg, R. L., Griffin, J. B., Kamath-Rayne, B. D., Harrison, M., Rouse, D. J., Moran, K., Hepler, B., Jobe, A. H. & McClure, E. M. (2016). Clinical interventions to reduce stillbirths in sub-Saharan Africa: a mathematical model to estimate the potential reduction of stillbirths associated with specific obstetric conditions. *BJOG*.
- [375] Punjabi, U., Wyns, C., Mahmoud, A., Vernelen, K., China, B. & Verheyen, G. (2016). Fifteen years of Belgian experience with external quality assessment of semen analysis. *Andrology* **4**, 1084-1093.
- [376] Trompoukis, C., Kalaitzis, C., Giannakopoulos, S., Sofikitis, N. & Touloupidis, S. (2007). Semen and the diagnosis of infertility in Aristotle. *Andrologia* **39**, 33-7.
- [377] Jungwirth, A., Diemer, T., Dohle, G. R., Giwercman, A., Kopa, Z., Krausz, C. & Tournaye, H. (2015). *Guidelines on Male Infertility*. Eur Assoc Urol.
- [378] Mändar, R., Punab, M., Borovkova, N., Lapp, E., Kiiker, R., Korrovits, P., Metspalu, A., Krjutškov, K., Nõlvak, H., Preem, J. K., Oopkaup, K., Salumets, A. & Truu, J. (2015). Complementary seminovaginal microbiome in couples. *Res Microbiol* **166**, 440-7.
- [379] Fowlkes, D. M., MacLeod, J. & O'Leary, W. M. (1975). T-mycoplasmas and human infertility: correlation of infection with alterations in seminal parameters. *Fertil Steril* **26**, 1212-8.
- [380] Fowlkes, D. M., Doohar, G. B. & O'Leary, W. M. (1975). Evidence by scanning electron microscopy for an association between spermatozoa and T-mycoplasmas in men of infertile marriage. *Fertil Steril* **26**, 1203-11.
- [381] Rehewy, M. S., Hafez, E. S., Thomas, A. & Brown, W. J. (1979). Aerobic and anaerobic bacterial flora in semen from fertile and infertile groups of men. *Arch Androl* **2**, 263-8.
- [382] Swenson, C. E., Toth, A., Toth, C., Wolfgruber, L. & O'Leary, W. M. (1980). Asymptomatic bacteriospermia in infertile men. *Andrologia* **12**, 7-11.

- [383] Mogra, N., Dhruva, A. & Kothari, L. K. (1981). Non-specific seminal tract infection and male infertility: a bacteriological study. *J Postgrad Med* **27**, 99-104.
- [384] Busolo, F., Zanchetta, R., Lanzone, E. & Cusinato, R. (1984). Microbial flora in semen of asymptomatic infertile men. *Andrologia* **16**, 269-75.
- [385] Naessens, A., Foulon, W., Debrucker, P., Devroey, P. & Lauwers, S. (1986). Recovery of microorganisms in semen and relationship to semen evaluation. *Fertil Steril* **45**, 101-5.
- [386] Eggert-Kruse, W., Rohr, G., Strock, W., Pohl, S., Schwalbach, B. & Runnebaum, B. (1995). Anaerobes in ejaculates of subfertile men. *Hum Reprod Update* **1**, 462-78.
- [387] Merino, G., Carranza-Lira, S., Murrieta, S., Rodriguez, L., Cuevas, E. & Moran, C. (1995). Bacterial infection and semen characteristics in infertile men. *Arch Androl* **35**, 43-7.
- [388] Jarvi, K., Lacroix, J. M., Jain, A., Dumitru, I., Heritz, D. & Mittelman, M. W. (1996). Polymerase chain reaction-based detection of bacteria in semen. *Fertil Steril* **66**, 463-7.
- [389] Lacroix, J. M., Jarvi, K., Batra, S. D., Heritz, D. M. & Mittelman, M. W. (1996). PCR-based technique for the detection of bacteria in semen and urine. *J Microbiol Meth* **26**, 61-71.
- [390] Byrn, R. A. & Kiessling, A. A. (1998). Analysis of human immunodeficiency virus in semen: indications of a genetically distinct virus reservoir. *J Reprod Immunol* **41**, 161-76.
- [391] Cardoso, E. M., Santoianni, J. E., De Paulis, A. N., Andrada, J. A., Predari, S. C. & Arregger, A. L. (1998). Improvement of semen quality in infected asymptomatic infertile male after bacteriological cure. *Medicina (B Aires)* **58**, 160-4.
- [392] Köhn, F. M., Erdmann, I., Oeda, T., el Mulla, K. F., Schiefer, H. G. & Schill, W. B. (1998). Influence of urogenital infections on sperm functions. *Andrologia* **30 Suppl 1**, 73-80.
- [393] Onemu, S. O. & Ibeh, I. N. (2001). Studies on the significance of positive bacterial semen cultures in male fertility in Nigeria. *Int J Fertil Womens Med* **46**, 210-4.
- [394] Esfandiari, N., Saleh, R. A., Abdoos, M., Rouzrokh, A. & Nazemian, Z. (2002). Positive bacterial culture of semen from infertile men with asymptomatic leukocytospermia. *Int J Fertil Womens Med* **47**, 265-70.
- [395] Sanocka, D., Fraczek, M., Jedrzejczak, P., Szumala-Kakol, A. & Kurpisz, M. (2004). Male genital tract infection: an influence of leukocytes and bacteria on semen. *J Reprod Immunol* **62**, 111-24.
- [396] Sanocka-Maciejewska, D., Ciupińska, M. & Kurpisz, M. (2005). Bacterial infection and semen quality. *J Reprod Immunol* **67**, 51-6.
- [397] Gdoura, R., Kchaou, W., Chaari, C., Znazen, A., Keskes, L., Rebai, T. & Hammami, A. (2007). *Ureaplasma urealyticum*, *Ureaplasma parvum*, *Mycoplasma hominis* and *Mycoplasma genitalium* infections and semen quality of infertile men. *BMC Infect Dis* **7**, 129.
- [398] Ikechukwu, O., George, E., Sabinus, A. E. & Florence, O. (2007). Role of enriched media in bacterial isolation from semen and effect of microbial infection on semen quality: A study on 100 infertile men. *Pakistan Journal of Medical Sciences* **23**, 885-888.
- [399] Kiessling, A. A., Desmarais, B. M., Yin, H. Z., Loverde, J. & Eyre, R. C. (2008). Detection and identification of bacterial DNA in semen. *Fertil Steril* **90**, 1744-56.
- [400] Pellati, D., Mylonakis, I., Bertoloni, G., Fiore, C., Andrisani, A., Ambrosini, G. & Armanini, D. (2008). Genital tract infections and infertility. *Eur J Obstet Gynecol Reprod Biol* **140**, 3-11.
- [401] Moretti, E., Capitani, S., Figura, N., Pammolli, A., Federico, M. G., Giannerini, V. & Collodel, G. (2009). The presence of bacteria species in semen and sperm quality. *J Assist Reprod Genet* **26**, 47-56.
- [402] Kokab, A., Akhondi, M. M., Sadeghi, M. R., Modarresi, M. H., Aarabi, M., Jennings, R., Pacey, A. A. & Eley, A. (2010). Raised inflammatory markers in semen from men with asymptomatic chlamydial infection. *J Androl* **31**, 114-20.
- [403] Onemu, S. O., Ogbimi, A. O. & Ophori, E. A. (2010). Microbiology and semen indices of sexually-active males in Benin City, Edo State, Nigeria. *J Bacteriol Res* **2**, 55-59.
- [404] Uneke, C. J. & Ugwuoru, C. D. (2010). Antibiotic susceptibility of urogenital microbial profile of infertile men in South-eastern Nigeria. *Andrologia* **42**, 268-73.
- [405] Momoh, A. R. M., Idonije, B. O., 3Nwoke, E.O., Osifo, U. C., Okhai, O., Omoroguiwa, A. & Momoh, A. A. (2011). Pathogenic bacteria-a probable cause of primary infertility among couples in Ekpoma. *J Microbiol Biotechnol Res* **1**, 66-71.

- [406] De Francesco, M. A., Negrini, R., Ravizzola, G., Galli, P. & Manca, N. (2011). Bacterial species present in the lower male genital tract: a five-year retrospective study. *Eur J Contracept Reprod Health Care* **16**, 47-53.
- [407] Hamada, A., Agarwal, A., Sharma, R., French, D. B., Ragheb, A. & Sabanegh, E. S., Jr. (2011). Empirical treatment of low-level leukocytospermia with doxycycline in male infertility patients. *Urology* **78**, 1320-5.
- [408] Isaiah, I. N., Nche, B. T., Nwagu, I. G. & Nnanna, I. I. (2011). Current studies on bacterospermia the leading cause of male infertility: a protégé and potential threat towards mans extinction. *N Am J Med Sci* **3**, 562-564.
- [409] La Vignera, S., Vicari, E., Condorelli, R. A., D'Agata, R. & Calogero, A. E. (2011). Male accessory gland infection and sperm parameters (review). *Int J Androl* **34**, e330-47.
- [410] Kaur, S. & Prabha, V. (2012). Infertility as a consequence of spermagglutinating *Staphylococcus aureus* colonization in genital tract of female mice. *PLoS One* **7**, e52325.
- [411] Rusz, A., Pilatz, A., Wagenlehner, F., Linn, T., Diemer, T., Schuppe, H. C., Lohmeyer, J., Hossain, H. & Weidner, W. (2012). Influence of urogenital infections and inflammation on semen quality and male fertility. *World J Urol* **30**, 23-30.
- [412] Salmeri, M., Valenti, D., La Vignera, S., Bellanca, S., Morello, A., Toscano, M. A., Mastrojeni, S. & Calogero, A. E. (2012). Prevalence of *Ureaplasma urealyticum* and *Mycoplasma hominis* infection in unselected infertile men. *J Chemother* **24**, 81-6.
- [413] Nabi, A., Khalili, M. A., Halvaei, I., Ghasemzadeh, J. & Zare, E. (2013). Seminal bacterial contaminations: Probable factor in unexplained recurrent pregnancy loss. *Iran J Reprod Med* **11**, 925-32.
- [414] Sleha, R., Boštíková, V., Salavec, M., Mosio, P., Kusáková, E., Kukla, R., Mazurová, J. & Šplíňo, M. (2013). Bacterial infection as a cause of infertility in humans(paper in Czech). *Epidemiol Mikrobiol Imunol* **62**, 26-32.
- [415] La Vignera, S., Condorelli, R. A., Vicari, E., Salmeri, M., Morgia, G., Favilla, V., Cimino, S. & Calogero, A. E. (2014). Microbiological investigation in male infertility: a practical overview. *J Med Microbiol* **63**, 1-14.
- [416] Weng, S. L., Chiu, C. M., Lin, F. M., Huang, W. C., Liang, C., Yang, T., Yang, T. L., Liu, C. Y., Wu, W. Y., Chang, Y. A., Chang, T. H. & Huang, H. D. (2014). Bacterial communities in semen from men of infertile couples: metagenomic sequencing reveals relationships of seminal microbiota to semen quality. *PLoS One* **9**, e110152.
- [417] Fraczek, M. & Kurpisz, M. (2015). Mechanisms of the harmful effects of bacterial semen infection on ejaculated human spermatozoa: potential inflammatory markers in semen. *Folia Histochem Cytobiol* **53**, 201-17.
- [418] Ruggeri, M., Cannas, S., Cubeddu, M., Molicotti, P., Piras, G. L., Dessole, S. & Zanetti, S. (2016). Bacterial agents as a cause of infertility in humans. *New Microbiol* **39**, 206-209.
- [419] Ahmadi, M. H., Mirsalehian, A., Sadighi Gilani, M. A., Bahador, A. & Talebi, M. (2017). Asymptomatic Infection With *Mycoplasma hominis* Negatively Affects Semen Parameters and Leads to Male Infertility as Confirmed by Improved Semen Parameters After Antibiotic Treatment. *Urology* **100**, 97-102.
- [420] Vander, H. & Prabha, V. (2015). Evaluation of fertility outcome as a consequence of intravaginal inoculation with sperm-impairing micro-organisms in a mouse model. *J Med Microbiol* **64**, 344-7.
- [421] Fraczek, M., Hryhorowicz, M., Gill, K., Zarzycka, M., Gaczarzewicz, D., Jedrzejczak, P., Bilinska, B., Piasecka, M. & Kurpisz, M. (2016). The effect of bacteriospermia and leukocytospermia on conventional and nonconventional semen parameters in healthy young normozoospermic males. *J Reprod Immunol* **118**, 18-27.
- [422] Shiadeh, M. N., Niyyati, M., Fallahi, S. & Rostami, A. (2016). Human parasitic protozoan infection to infertility: a systematic review. *Parasitol Res* **115**, 469-77.
- [423] Vicari, L. O., Castiglione, R., Salemi, M., Vicari, B. O., Mazzarino, M. C. & Vicari, E. (2016). Effect of levofloxacin treatment on semen hyperviscosity in chronic bacterial prostatitis patients. *Andrologia* **48**, 380-8.
- [424] Kjærgaard, N., Kristensen, B., Hansen, E. S., Farholt, S., Schønheyder, H. C., Uldbjerg, N. & Madsen, H. (1997). Microbiology of semen specimens from males attending a fertility clinic. *APMIS* **105**, 566-70.

- [425] Hillier, S. L., Rabe, L. K., Muller, C. H., Zarutskie, P., Kuzan, F. B. & Stenchever, M. A. (1990). Relationship of bacteriologic characteristics to semen indices in men attending an infertility clinic. *Obstet Gynecol* **75**, 800-4.
- [426] Dieterle, S. (2008). Urogenital infections in reproductive medicine. *Andrologia* **40**, 117-9.
- [427] Vilvanathan, S., Kandasamy, B., Jayachandran, A. L., Sathiyarayanan, S., Tanjore Singaravelu, V., Krishnamurthy, V. & Elangovan, V. (2016). Bacteriospermia and Its Impact on Basic Semen Parameters among Infertile Men. *Interdiscip Perspect Infect Dis* **2016**, 2614692.
- [428] Liversedge, N. H., Jenkins, J. M., Keay, S. D., McLaughlin, E. A., Al-Sufyan, H., Maile, L. A., Joels, L. A. & Hull, M. G. R. (1996). Antibiotic treatment based on seminal cultures from asymptomatic male partners in in-vitro fertilization is unnecessary and may be detrimental. *Hum Reprod* **11**, 1227-31.
- [429] Bhandari, P., Rishi, P. & Prabha, V. (2016). Positive effect of probiotic *Lactobacillus plantarum* in reversing the LPS induced infertility in mouse model. *J Med Microbiol* **65**, 345-350.
- [430] Hou, D., Zhou, X., Zhong, X., Settles, M. L., Herring, J., Wang, L., Abdo, Z., Forney, L. J. & Xu, C. (2013). Microbiota of the seminal fluid from healthy and infertile men. *Fertil Steril* **100**, 1261-9.
- [431] Javurek, A. B., Spollen, W. G., Ali, A. M. M., Johnson, S. A., Lubahn, D. B., Bivens, N. J., Bromert, K. H., Ellersieck, M. R., Givan, S. A. & Rosenfeld, C. S. (2016). Discovery of a novel seminal fluid microbiome and influence of estrogen receptor alpha genetic status. *Scientific Reports* **6**.
- [432] Craig, L. B., Peck, J. D., Xu, J., Sankaranarayanan, K., Warinner, C., Hansen, K. R., Anderson, M. & Lewis, C. M. (2015). Characterizing the Semen Microbiome and Associations with Semen Parameters: The Chasm Study. *Fertil Steril* **104**, E66-E66.
- [433] Deen, G. F., Knust, B., Broutet, N., Sesay, F. R., Formenty, P., Ross, C., Thorson, A. E., Massaquoi, T. A., Marrinan, J. E., Ervin, E., Jambai, A., McDonald, S. L., Bernstein, K., Wurie, A. H., Dumbuya, M. S., Abad, N., Idriss, B., Wi, T., Bennett, S. D., Davies, T., Ebrahim, F. K., Meites, E., Naidoo, D., Smith, S., Banerjee, A., Erickson, B. R., Brault, A., Durski, K. N., Winter, J., Sealy, T., Nichol, S. T., Lamunu, M., Stroher, U., Morgan, O. & Sahr, F. (2015). Ebola RNA Persistence in Semen of Ebola Virus Disease Survivors - Preliminary Report. *N Engl J Med*.
- [434] Soka, M. J., Choi, M. J., Baller, A., White, S., Rogers, E., Purpura, L. J., Mahmoud, N., Wasunna, C., Massaquoi, M., Abad, N., Kollie, J., Dweh, S., Bemah, P. K., Christie, A., Ladele, V., Subah, O. C., Pillai, S., Mugisha, M., Kpaka, J., Kowalewski, S., German, E., Stenger, M., Nichol, S., Stroher, U., Vanderende, K. E., Zarecki, S. M., Green, H. H., Bailey, J. A., Rollin, P., Marston, B., Nyenswah, T. G., Gasasira, A., Knust, B. & Williams, D. (2016). Prevention of sexual transmission of Ebola in Liberia through a national semen testing and counselling programme for survivors: an analysis of Ebola virus RNA results and behavioural data. *Lancet Glob Health* **4**, e736-43.
- [435] Thorson, A., Formenty, P., Lofthouse, C. & Broutet, N. (2016). Systematic review of the literature on viral persistence and sexual transmission from recovered Ebola survivors: evidence and recommendations. *BMJ Open* **6**, e008859.
- [436] Sissoko, D., Duraffour, S., Kerber, R., Kolie, J. S., Beavogui, A. H., Camara, A. M., Colin, G., Rieger, T., Oestereich, L., Palyi, B., Wurr, S., Guedj, J., Nguyen, T. H., Eggo, R. M., Watson, C. H., Edmunds, W. J., Bore, J. A., Koundouno, F. R., Cabeza-Cabrerizo, M., Carter, L. L., Kafetzopoulou, L. E., Kuisma, E., Michel, J., Patrono, L. V., Rickett, N. Y., Singethan, K., Rudolf, M., Lander, A., Pallasch, E., Bockholt, S., Rodriguez, E., Di Caro, A., Wolfel, R., Gabriel, M., Gurry, C., Formenty, P., Keita, S., Malvy, D., Carroll, M. W., Anglaret, X. & Gunther, S. (2017). Persistence and clearance of Ebola virus RNA from seminal fluid of Ebola virus disease survivors: a longitudinal analysis and modelling study. *Lancet Glob Health* **5**, e80-e88.
- [437] Klatt, N. R., Cheu, R., Birse, K., Zevin, A. S., Perner, M., Noël-Romas, L., Grobler, A., Westmacott, G., Xie, I. Y., Butler, J., Mansoor, L., McKinnon, L. R., Passmore, J. S., Abdool Karim, Q., Abdool Karim, S. S. & Burgener, A. D. (2017). Vaginal bacteria modify HIV tenofovir microbicide efficacy in African women. *Science* **356**, 938-945.

- [438] Ma, W., Li, S., Ma, S., Jia, L., Zhang, F., Zhang, Y., Zhang, J., Wong, G., Zhang, S., Lu, X., Liu, M., Yan, J., Li, W., Qin, C., Han, D., Qin, C., Wang, N., Li, X. & Gao, G. F. (2016). Zika Virus Causes Testis Damage and Leads to Male Infertility in Mice. *Cell* **167**, 1511-1524 e10.
- [439] Baud, D., Musso, D., Vouga, M., Alves, M. P. & Vulliemoz, N. (2017). Zika virus: A new threat to human reproduction. *Am J Reprod Immunol* **77**.
- [440] Hamer, D. H., Wilson, M. E., Jean, J. & Chen, L. H. (2017). Epidemiology, Prevention, and Potential Future Treatments of Sexually Transmitted Zika Virus Infection. *Curr Infect Dis Rep* **19**, 16.
- [441] Ohri, M. & Prabha, V. (2005). Isolation of a sperm-agglutinating factor from *Staphylococcus aureus* isolated from a woman with unexplained infertility. *Fertil Steril* **84**, 1539-41.
- [442] Diemer, T., Huwe, P., Ludwig, M., Hauck, E. W. & Weidner, W. (2003). Urogenital infection and sperm motility. *Andrologia* **35**, 283-7.
- [443] Prabha, V., Sandhu, R., Kaur, S., Kaur, K., Sarwal, A., Mavuduru, R. S. & Singh, S. K. (2010). Mechanism of sperm immobilization by *Escherichia coli*. *Adv Urol* **2010**, 240268.
- [444] Fraczek, M., Wiland, E., Piasecka, M., Boksa, M., Gaczarzewicz, D., Szumala-Kakol, A., Kolanowski, T., Beutin, L. & Kurpisz, M. (2014). Fertilizing potential of ejaculated human spermatozoa during in vitro semen bacterial infection. *Fertil Steril* **102**, 711-719 e1.
- [445] Kaur, K. & Prabha, V. (2014). Spermagglutinating *Escherichia coli* and its role in infertility: in vivo study. *Microb Pathog* **69-70**, 33-8.
- [446] Pretorius, E., Mbotwe, S., Bester, J., Robinson, C. J. & Kell, D. B. (2016). Acute induction of anomalous and amyloidogenic blood clotting by molecular amplification of highly substoichiometric levels of bacterial lipopolysaccharide. *J R Soc Interface* **123**, 20160539.
- [447] Kell, D. B. & Pretorius, E. (2017). Proteins behaving badly. Substoichiometric molecular control and amplification of the initiation and nature of amyloid fibril formation: lessons from and for blood clotting. *Progr Biophys Mol Biol* **123**, 16-41.
- [448] Pretorius, E., Page, M. J., Hendricks, L., Nkosi, N. B., Benson, S. R. & Kell, D. B. (2017). Both lipopolysaccharide and lipoteichoic acids potently induce anomalous fibrin amyloid formation: assessment with novel Amytracker™ stains. bioRxiv preprint. *bioRxiv*, 143867.
- [449] Gupta, S. & Prabha, V. (2012). Human Sperm Interaction with *Staphylococcus aureus*: A Molecular Approach. *J Pathog* **2012**, 816536.
- [450] Enwuru, C. A., Iwalokun, B., Enwuru, V. N., Ezechi, O. & Oluwadun, A. (2016). The effect of presence of facultative bacteria species on semen and sperm quality of men seeking fertility care. *African J Urol* **22**, 213-222.
- [451] Pandian, Z., Bhattacharya, S. & Templeton, A. (2001). Review of unexplained infertility and obstetric outcome: a 10 year review. *Hum Reprod* **16**, 2593-7.
- [452] Trogstad, L., Magnus, P., Moffett, A. & Stoltenberg, C. (2009). The effect of recurrent miscarriage and infertility on the risk of pre-eclampsia. *BJOG* **116**, 108-13.
- [453] Basso, O. & Baird, D. D. (2003). Infertility and preterm delivery, birthweight, and Caesarean section: a study within the Danish National Birth Cohort. *Hum Reprod* **18**, 2478-84.
- [454] Basso, O., Weinberg, C. R., Baird, D. D., Wilcox, A. J. & Olsen, J. (2003). Subfecundity as a correlate of preeclampsia: A study within the Danish National Birth Cohort. *Am J Epidemiol* **157**, 195-202.
- [455] Sohrabvand, F., Jafari, M., Shariat, M., Haghollahi, F. & Lotfi, M. (2015). Frequency and epidemiologic aspects of male infertility. *Acta Med Iran* **53**, 231-5.
- [456] Dobson, P. D. & Kell, D. B. (2008). Carrier-mediated cellular uptake of pharmaceutical drugs: an exception or the rule? *Nat Rev Drug Disc* **7**, 205-220.
- [457] Kell, D. B., Dobson, P. D., Bilsland, E. & Oliver, S. G. (2013). The promiscuous binding of pharmaceutical drugs and their transporter-mediated uptake into cells: what we (need to) know and how we can do so. *Drug Disc Today* **18**, 218-239.
- [458] Kell, D. B. & Oliver, S. G. (2014). How drugs get into cells: tested and testable predictions to help discriminate between transporter-mediated uptake and lipoidal bilayer diffusion. *Front Pharmacol* **5**, 231.
- [459] Pajovic, B., Radojevic, N., Vukovic, M. & Stjepcevic, A. (2013). Semen analysis before and after antibiotic treatment of asymptomatic chlamydia- and ureaplasma-related pyospermia. *Andrologia* **45**, 266-271.

- [460] Schoor, R. A. (2002). Prostatitis and male infertility: evidence and links. *Curr Urol Rep* **3**, 324-9.
- [461] Everaert, K., Mahmoud, A., Depuydt, C., Maeyaert, M. & Comhaire, F. (2003). Chronic prostatitis and male accessory gland infection--is there an impact on male infertility (diagnosis and therapy)? *Andrologia* **35**, 325-30.
- [462] La Vignera, S., Condorelli, R., Vicari, E., D'Agata, R. & Calogero, A. E. (2012). High frequency of sexual dysfunction in patients with male accessory gland infections. *Andrologia* **44 Suppl 1**, 438-46.
- [463] Alshahrani, S., McGill, J. & Agarwal, A. (2013). Prostatitis and male infertility. *J Reprod Immunol* **100**, 30-6.
- [464] La Vignera, S., Vicari, E., Condorelli, R. A., Franchina, C., Scalia, G., Morgia, G., Perino, A., Schillaci, R. & Calogero, A. E. (2015). Prevalence of human papilloma virus infection in patients with male accessory gland infection. *Reprod Biomed Online* **30**, 385-91.
- [465] Estemalik, J., Demko, C., Bissada, N. F., Joshi, N., Bodner, D., Shankar, E. & Gupta, S. (2017). Simultaneous detection of oral pathogens in subgingival plaque and prostatic fluid of men with periodontal and prostatic diseases. *J Periodontol*, 1-11.
- [466] Hedger, M. P. (2011). Toll-like receptors and signalling in spermatogenesis and testicular responses to inflammation--a perspective. *J Reprod Immunol* **88**, 130-41.
- [467] Bhushan, S., Schuppe, H. C., Fijak, M. & Meinhardt, A. (2009). Testicular infection: microorganisms, clinical implications and host-pathogen interaction. *J Reprod Immunol* **83**, 164-7.
- [468] Bhushan, S., Schuppe, H. C., Tchatalbachev, S., Fijak, M., Weidner, W., Chakraborty, T. & Meinhardt, A. (2009). Testicular innate immune defense against bacteria. *Mol Cell Endocrinol* **306**, 37-44.
- [469] Chen, B., Yu, L., Wang, J., Li, C., Zhao, K. & Zhang, H. (2016). Involvement of Prokineticin 2 and Prokineticin Receptor 1 in Lipopolysaccharide-Induced Testitis in Rats. *Inflammation* **39**, 534-42.
- [470] Lipsky, B. A. (1999). Prostatitis and urinary tract infection in men: what's new; what's true? *Am J Med* **106**, 327-34.
- [471] Lipsky, B. A., Byren, I. & Hoey, C. T. (2010). Treatment of bacterial prostatitis. *Clin Infect Dis* **50**, 1641-52.
- [472] Vicari, E., Calogero, A. E., Condorelli, R. A., Vicari, L. O. & La Vignera, S. (2012). Male accessory gland infection frequency in infertile patients with chronic microbial prostatitis and irritable bowel syndrome. *Int J Androl* **35**, 183-9.
- [473] Wagenlehner, F. M. E., Pilatz, A., Bschleipfer, T., Diemer, T., Linn, T., Meinhardt, A., Schagdarsurengin, U., Dansranjav, T., Schuppe, H. C. & Weidner, W. (2013). Bacterial prostatitis. *World J Urol* **31**, 711-6.
- [474] Krebs, J., Bartel, P. & Pannek, J. (2014). Chronic bacterial prostatitis in men with spinal cord injury. *World J Urol* **32**, 1579-85.
- [475] Krebs, J., Bartel, P. & Pannek, J. (2014). Bacterial persistence in the prostate after antibiotic treatment of chronic bacterial prostatitis in men with spinal cord injury. *Urology* **83**, 515-20.
- [476] Wagenlehner, F. M. E., Weidner, W., Pilatz, A. & Naber, K. G. (2014). Urinary tract infections and bacterial prostatitis in men. *Curr Opin Infect Dis* **27**, 97-101.
- [477] Gill, B. C. & Shoskes, D. A. (2016). Bacterial prostatitis. *Curr Opin Infect Dis* **29**, 86-91.
- [478] Krieger, J. N. & Thumbikat, P. (2016). Bacterial Prostatitis: Bacterial Virulence, Clinical Outcomes, and New Directions. *Microbiol Spectr* **4**.
- [479] Videčnik Zorman, J., Matičič, M., Jeverica, S. & Smrkolj, T. (2015). Diagnosis and treatment of bacterial prostatitis. *Acta Dermatovenereol* **24**, 25-29.
- [480] Condorelli, R. A., Vicari, E., Mongioi, L. M., Russo, G. I., Morgia, G., La Vignera, S. & Calogero, A. E. (2016). Human Papilloma Virus Infection in Patients with Male Accessory Gland Infection: Usefulness of the Ultrasound Evaluation. *Int J Endocrinol* **2016**, 9174609.
- [481] Alvarado-Esquivel, C., Pacheco-Vega, S. J., Hernández-Tinoco, J., Centeno-Tinoco, M. M., Beristain-Garcia, I., Sánchez-Anguiano, L. F., Liesenfeld, O., Rabago-Sánchez, E. & Berumen-Segovia, L. O. (2014). Miscarriage history and *Toxoplasma gondii* infection: A cross-sectional study in women in Durango City, Mexico. *Eur J Microbiol Immunol (Bp)* **4**, 117-22.

- [482] Giakoumelou, S., Wheelhouse, N., Cuschieri, K., Entrican, G., Howie, S. E. M. & Horne, A. W. (2015). The role of infection in miscarriage. *Hum Reprod Update*.
- [483] van der Eijk, A. A., van Genderen, P. J., Verdijs, R. M., Reusken, C. B., Mogling, R., van Kampen, J. J., Widagdo, W., Aron, G. I., GeurtsvanKessel, C. H., Pas, S. D., Raj, V. S., Haagmans, B. L. & Koopmans, M. P. (2016). Miscarriage Associated with Zika Virus Infection. *N Engl J Med* **375**, 1002-4.
- [484] McDonald, H. M. & Chambers, H. M. (2000). Intrauterine infection and spontaneous midgestation abortion: is the spectrum of microorganisms similar to that in preterm labor? *Infect Dis Obstet Gynecol* **8**, 220-7.
- [485] Romero, R., Espinoza, J. & Mazor, M. (2004). Can endometrial infection/inflammation explain implantation failure, spontaneous abortion, and preterm birth after in vitro fertilization? *Fertil Steril* **82**, 799-804.
- [486] Conde-Ferrández, L., Chan May, A. d. A., Carrillo-Martínez, J. R., Ayora-Talavera, G. & González-Losa, M. d. R. (2013). Human papillomavirus infection and spontaneous abortion: a case-control study performed in Mexico. *Eur J Obstet Gynecol Reprod Biol* **170**, 468-73.
- [487] Wang, H., Cao, Q., Ge, J., Liu, C., Ma, Y., Meng, Y., Wang, Y., Zhao, X., Liu, R., Li, C., Wang, Y., Zhong, J., Ju, W., Jenkins, E. C., Brown, W. T. & Zhong, N. (2014). LncRNA-regulated infection and inflammation pathways associated with pregnancy loss: genome wide differential expression of lncRNAs in early spontaneous abortion. *Am J Reprod Immunol* **72**, 359-75.
- [488] Ahmadi, A., Khodabandehloo, M., Ramazanzadeh, R., Farhadifar, F., Roshani, D., Ghaderi, E. & Farhangi, N. (2016). The Relationship between *Chlamydia trachomatis* Genital Infection and Spontaneous Abortion. *J Reprod Infertil* **17**, 110-6.
- [489] Ambühl, L. M. M., Baandrup, U., Dybkaer, K., Blaakaer, J., Uldbjerg, N. & Sørensen, S. (2016). Human Papillomavirus Infection as a Possible Cause of Spontaneous Abortion and Spontaneous Preterm Delivery. *Infect Dis Obstet Gynecol* **2016**, 3086036.
- [490] Golding, B., Scott, D. E., Scharf, O., Huang, L. Y., Zaitseva, M., Lapham, C., Eller, N. & Golding, H. (2001). Immunity and protection against *Brucella abortus*. *Microbes Infect* **3**, 43-8.
- [491] Corbel, M. J., Elberg, S. S. & Cosivi, O. (2006). *Brucellosis in humans and animals*. World Health Organization, Geneva.
- [492] Oliveira, S. C., de Oliveira, F. S., Macedo, G. C., de Almeida, L. A. & Carvalho, N. B. (2008). The role of innate immune receptors in the control of *Brucella abortus* infection: toll-like receptors and beyond. *Microbes Infect* **10**, 1005-9.
- [493] Kuster, C. E. & Althouse, G. C. (2016). The impact of bacteriospermia on boar sperm storage and reproductive performance. *Theriogenology* **85**, 21-6.
- [494] Dorneles, E. M. S., Sriranganathan, N. & Lage, A. P. (2015). Recent advances in *Brucella abortus* vaccines. *Vet Res* **46**, 76.
- [495] Brown, V. G., Schollum, L. M. & Jarvis, B. D. W. (1974). Microbiology of Bovine Semen and Artificial Breeding Practices under New-Zealand Conditions. *NZ J Agric Res* **17**, 431-432.
- [496] Schollum, L. M. (1977). The microbiology of bovine serum and the antimicrobial activity of bovine seminal plasma, Massey University.
- [497] Yániz, J. L., Marco-Aguado, M. A., Mateos, J. A. & Santolaria, P. (2010). Bacterial contamination of ram semen, antibiotic sensitivities, and effects on sperm quality during storage at 15 degrees C. *Anim Reprod Sci* **122**, 142-149.
- [498] Gączarzewicz, D., Udała, J., Piasecka, M., Błaszczuk, B. & Stankiewicz, T. (2016). Bacterial contamination of boar semen and its relationship to sperm quality preserved in commercial extender containing gentamicin sulfate. *Pol J Vet Sci* **19**, 451-459.
- [499] Romero, R., Mazor, M., Wu, Y. K., Sirtori, M., Oyarzun, E., Mitchell, M. D. & Hobbins, J. C. (1988). Infection in the pathogenesis of preterm labor. *Semin Perinatol* **12**, 262-79.
- [500] Toth, M., Witkin, S. S., Ledger, W. & Thaler, H. (1988). The Role of Infection in the Etiology of Preterm Birth. *Obstet Gynecol* **71**, 723-726.
- [501] Cassell, G. H., Waites, K. B., Watson, H. L., Crouse, D. T. & Harasawa, R. (1993). *Ureaplasma urealyticum* intrauterine infection: role in prematurity and disease in newborns. *Clin Microbiol Rev* **6**, 69-87.
- [502] McGregor, J. A., French, J. I., Jones, W., Milligan, K., McKinney, P. J., Patterson, E. & Parker, R. (1994). Bacterial vaginosis is associated with prematurity and vaginal fluid

- mucinase and sialidase: results of a controlled trial of topical clindamycin cream. *Am J Obstet Gynecol* **170**, 1048-59; discussion 1059-60.
- [503] Lee, S. E., Romero, R., Kim, C. J., Shim, S. S. & Yoon, B. H. (2006). Funisitis in term pregnancy is associated with microbial invasion of the amniotic cavity and intra-amniotic inflammation. *J Matern Fetal Neonatal Med* **19**, 693-7.
- [504] Goldenberg, R. L., Hauth, J. C. & Andrews, W. W. (2000). Intrauterine infection and preterm delivery. *N Engl J Med* **342**, 1500-7.
- [505] Gonçalves, L. F., Chaiworapongsa, T. & Romero, R. (2002). Intrauterine infection and prematurity. *Ment Retard Dev Disabil Res Rev* **8**, 3-13.
- [506] Gerber, S., Vial, Y., Hohlfeld, P. & Witkin, S. S. (2003). Detection of *Ureaplasma urealyticum* in second-trimester amniotic fluid by polymerase chain reaction correlates with subsequent preterm labor and delivery. *J Infect Dis* **187**, 518-21.
- [507] Gardella, C., Riley, D. E., Hitti, J., Agnew, K., Krieger, J. N. & Eschenbach, D. (2004). Identification and sequencing of bacterial rDNAs in culture-negative amniotic fluid from women in premature labor. *Am J Perinatol* **21**, 319-23.
- [508] Check, J. H. (2010). A practical approach to the prevention of miscarriage Part 4-role of infection. *Clin Exp Obstet Gyn* **37**, 252-255.
- [509] Frey, H. A. & Klebanoff, M. A. (2016). The epidemiology, etiology, and costs of preterm birth. *Semin Fetal Neonatal Med* **21**, 68-73.
- [510] Nadeau, H. C. G., Subramaniam, A. & Andrews, W. W. (2016). Infection and preterm birth. *Semin Fetal Neonatal Med* **21**, 100-5.
- [511] Vinturache, A. E., Gyamfi-Bannerman, C., Hwang, J., Mysorekar, I. U., Jacobsson, B. & Preterm Birth International Collaborative (PREBIC). (2016). Maternal microbiome - A pathway to preterm birth. *Semin Fetal Neonatal Med* **21**, 94-9.
- [512] Espinoza, J., Erez, O. & Romero, R. (2006). Preconceptional antibiotic treatment to prevent preterm birth in women with a previous preterm delivery. *Am J Obstet Gynecol* **194**, 630-7.
- [513] Joergensen, J. S., Kjaer Weile, L. K. & Lamont, R. F. (2014). The early use of appropriate prophylactic antibiotics in susceptible women for the prevention of preterm birth of infectious etiology. *Expert Opin Pharmacother* **15**, 2173-91.
- [514] Goldenberg, R. L., Culhane, J. F., Iams, J. D. & Romero, R. (2008). Epidemiology and causes of preterm birth. *Lancet* **371**, 75-84.
- [515] Bastek, J. A., Gómez, L. M. & Elovitz, M. A. (2011). The role of inflammation and infection in preterm birth. *Clin Perinatol* **38**, 385-406.
- [516] Johnson, H. L., Ghanem, K. G., Zenilman, J. M. & Erbelding, E. J. (2011). Sexually transmitted infections and adverse pregnancy outcomes among women attending inner city public sexually transmitted diseases clinics. *Sex Transm Dis* **38**, 167-71.
- [517] Manzoni, P., Rizzollo, S., Decembrino, L., Ruffinazzi, G., Rossi Ricci, A., Gallo, E., Stolfi, I., Mostert, M., Stronati, M. & Farina, D. (2011). Recent advances in prevention of sepsis in the premature neonates in NICU. *Early Hum Dev* **87 Suppl 1**, S31-3.
- [518] Rours, G. I. J. G., Duijts, L., Moll, H. A., Arends, L. R., de Groot, R., Jaddoe, V. W., Hofman, A., Steegers, E. A. P., Mackenbach, J. P., Ott, A., Willemse, H. F. M., van der Zwaan, E. A. E., Verkooijen, R. P. & Verbrugh, H. A. (2011). *Chlamydia trachomatis* infection during pregnancy associated with preterm delivery: a population-based prospective cohort study. *Eur J Epidemiol* **26**, 493-502.
- [519] Jefferson, K. K. (2012). The bacterial etiology of preterm birth. *Adv Appl Microbiol* **80**, 1-22.
- [520] Shinar, S., Skornick-Rapaport, A. & Rimmon, E. (2012). Placental abruption remote from term associated with Q Fever infection. *Obstet Gynecol* **120**, 503-5.
- [521] Subramaniam, A., Abramovici, A., Andrews, W. W. & Tita, A. T. (2012). Antimicrobials for Preterm Birth Prevention: An Overview. *Infect Dis Obs Gynecol* **2012**.
- [522] Aagaard, K., Ma, J., Antony, K. M., Ganu, R., Petrosino, J. & Versalovic, J. (2014). The placenta harbors a unique microbiome. *Sci Transl Med* **6**, 237ra65.
- [523] Kacerovsky, M., Vrbicky, F., Kutova, R., Pliskova, L., Andrys, C., Musilova, I., Menon, R., Lamont, R. & Nekvindova, J. (2015). Cervical microbiota in women with preterm prelabor rupture of membranes. *PLoS One* **10**, e0126884.
- [524] Lamont, R. F. (2015). Advances in the Prevention of Infection-Related Preterm Birth. *Front Immunol* **6**, 566.

- [525] Lee, S. Y. R. & Leung, C. W. (2012). Histological chorioamnionitis - implication for bacterial colonization, laboratory markers of infection, and early onset sepsis in very-low-birth-weight neonates. *J Matern Fetal Neonatal Med* **25**, 364-8.
- [526] Lis, R., Rowhani-Rahbar, A. & Manhart, L. E. (2015). *Mycoplasma genitalium* infection and female reproductive tract disease: a meta-analysis. *Clin Infect Dis* **61**, 418-26.
- [527] Allen-Daniels, M. J., Serrano, M. G., Pflugner, L. P., Fettweis, J. M., Prestosa, M. A., Koparde, V. N., Brooks, J. P., Strauss, J. F., Romero, R., Chaiworapongsa, T., Eschenbach, D. A., Buck, G. A. & Jefferson, K. K. (2015). Identification of a gene in *Mycoplasma hominis* associated with preterm birth and microbial burden in intraamniotic infection. *Am J Obstet Gynecol* **212**.
- [528] de Andrade Ramos, B., Kanninen, T. T., Sisti, G. & Witkin, S. S. (2015). Microorganisms in the female genital tract during pregnancy: tolerance versus pathogenesis. *Am J Reprod Immunol* **73**, 383-9.
- [529] Pammi, M. & Weisman, L. E. (2015). Late-onset sepsis in preterm infants: update on strategies for therapy and prevention. *Expert Rev Anti Infect Ther* **13**, 487-504.
- [530] Ueno, T., Niimi, H., Yoneda, N., Yoneda, S., Mori, M., Tabata, H., Minami, H., Saito, S. & Kitajima, I. (2015). Eukaryote-Made Thermostable DNA Polymerase Enables Rapid PCR-Based Detection of Mycoplasma, Ureaplasma and Other Bacteria in the Amniotic Fluid of Preterm Labor Cases. *PLoS One* **10**, e0129032.
- [531] Yoneda, S., Shiozaki, A., Yoneda, N., Ito, M., Shima, T., Fukuda, K., Ueno, T., Niimi, H., Kitajima, I., Kigawa, M. & Saito, S. (2016). Antibiotic Therapy Increases the Risk of Preterm Birth in Preterm Labor without Intra-Amniotic Microbes, but may Prolong the Gestation Period in Preterm Labor with Microbes, Evaluated by Rapid and High-Sensitive PCR System. *Am J Reprod Immunol* **75**, 440-50.
- [532] García-Velasco, J. A., Menabrito, M. & Catalán, I. B. (2017). What fertility specialists should know about the vaginal microbiome: a review. *Reproductive BioMedicine Online*.
- [533] van Well, G. T. J., Daalderop, L. A., Wolfs, T. & Kramer, B. W. (2017). Human perinatal immunity in physiological conditions and during infection. *Mol Cell Pediatr* **4**, 4.
- [534] Zini, A., Boman, J. M., Belzile, E. & Ciampi, A. (2008). Sperm DNA damage is associated with an increased risk of pregnancy loss after IVF and ICSI: systematic review and meta-analysis. *Hum Reprod* **23**, 2663-8.
- [535] Gil-Villa, A. M., Cardona-Maya, W., Agarwal, A., Sharma, R. & Cadavid, Á. (2010). Assessment of sperm factors possibly involved in early recurrent pregnancy loss. *Fertil Steril* **94**, 1465-72.
- [536] Brahem, S., Mehdi, M., Landolsi, H., Mougou, S., Elghezal, H. & Saad, A. (2011). Semen parameters and sperm DNA fragmentation as causes of recurrent pregnancy loss. *Urology* **78**, 792-6.
- [537] Shina, A. & Carp, H. J. A. (2012). Recurrent pregnancy loss - beyond evidence based medicine. *Gynecol Endocrinol* **28**, 991-2.
- [538] Lewis, S. E. M., John Aitken, R., Conner, S. J., Iuliis, G. D., Evenson, D. P., Henkel, R., Giwercman, A. & Gharagozloo, P. (2013). The impact of sperm DNA damage in assisted conception and beyond: recent advances in diagnosis and treatment. *Reprod Biomed Online* **27**, 325-37.
- [539] Simon, L., Proutski, I., Stevenson, M., Jennings, D., McManus, J., Lutton, D. & Lewis, S. E. M. (2013). Sperm DNA damage has a negative association with live-birth rates after IVF. *Reprod Biomed Online* **26**, 68-78.
- [540] Wang, R., Zhou, H., Zhang, Z., Dai, R., Geng, D. & Liu, R. (2013). The impact of semen quality, occupational exposure to environmental factors and lifestyle on recurrent pregnancy loss. *J Assist Reprod Genet* **30**, 1513-8.
- [541] Belloc, S., Benkhalifa, M., Cohen-Bacrie, M., Dalleac, A., Chahine, H., Amar, E. & Zini, A. (2014). Which isolated sperm abnormality is most related to sperm DNA damage in men presenting for infertility evaluation. *J Assist Reprod Genet* **31**, 527-32.
- [542] Bonney, E. A. & Brown, S. A. (2014). To drive or be driven: the path of a mouse model of recurrent pregnancy loss. *Reproduction* **147**, R153-67.
- [543] Kavitha, P. & Malini, S. S. (2014). Positive association of sperm dysfunction in the pathogenesis of recurrent pregnancy loss. *J Clin Diagn Res* **8**, OC07-10.

- [544] Zhao, J., Zhang, Q., Wang, Y. & Li, Y. (2014). Whether sperm deoxyribonucleic acid fragmentation has an effect on pregnancy and miscarriage after in vitro fertilization/intracytoplasmic sperm injection: a systematic review and meta-analysis. *Fertil Steril* **102**, 998-1005 e8.
- [545] Bronson, R. (2015). The Male Role in Pregnancy Loss and Embryo Implantation Failure, vol. 868. Springer, Berlin.
- [546] Esteves, S. C., Sánchez-Martin, F., Sánchez-Martin, P., Schneider, D. T. & Gosálvez, J. (2015). Comparison of reproductive outcome in oligozoospermic men with high sperm DNA fragmentation undergoing intracytoplasmic sperm injection with ejaculated and testicular sperm. *Fertil Steril* **104**, 1398-405.
- [547] Zidi-Jrah, I., Hajlaoui, A., Mougou-Zerelli, S., Kammoun, M., Meniaoui, I., Sallem, A., Brahém, S., Fekih, M., Bibi, M., Saad, A. & Ibalá-Romdhane, S. (2016). Relationship between sperm aneuploidy, sperm DNA integrity, chromatin packaging, traditional semen parameters, and recurrent pregnancy loss. *Fertil Steril* **105**, 58-64.
- [548] Simon, L., Zini, A., Dyachenko, A., Ciampi, A. & Carrell, D. T. (2017). A systematic review and meta-analysis to determine the effect of sperm DNA damage on in vitro fertilization and intracytoplasmic sperm injection outcome. *Asian J Androl* **19**, 80-90.
- [549] Agarwal, A., Majzoub, A., Esteves, S. C., Ko, E., Ramasamy, R. & Zini, A. (2016). Clinical utility of sperm DNA fragmentation testing: practice recommendations based on clinical scenarios. *Transl Androl Urol* **5**, 935-950.
- [550] Usmani, S., Liu, H. C., Pilcher, C. D., Witkowska, H. E., Kirchhoff, F., Greene, W. C., Munch, J. & Roan, N. R. (2014). HIV-enhancing Amyloids Are Prevalent in Fresh Semen and Are a Determinant for Semen's Ability to Enhance HIV Infection: Relevance for HIV Transmission. *AIDS Res Hum Retroviruses* **30**, A183-A184.
- [551] Binder, N. K., Sheedy, J. R., Hannan, N. J. & Gardner, D. K. (2015). Male obesity is associated with changed spermatozoa Cox4i1 mRNA level and altered seminal vesicle fluid composition in a mouse model. *Mol Hum Reprod* **21**, 424-34.
- [552] Gil-Villa, A. M., Cardona-Maya, W., Agarwal, A., Sharma, R. & Cadavid, Á. (2009). Role of male factor in early recurrent embryo loss: do antioxidants have any effect? *Fertil Steril* **92**, 565-71.
- [553] Shiva, M., Gautam, A. K., Verma, Y., Shivgotra, V., Doshi, H. & Kumar, S. (2011). Association between sperm quality, oxidative stress, and seminal antioxidant activity. *Clin Biochem* **44**, 319-24.
- [554] Agarwal, A., Durairajanayagam, D., Halabi, J., Peng, J. & Vazquez-Levin, M. (2014). Proteomics, oxidative stress and male infertility. *Reprod Biomed Online* **29**, 32-58.
- [555] Durairajanayagam, D., Agarwal, A., Ong, C. & Prashast, P. (2014). Lycopene and male infertility. *Asian J Androl* **16**, 420-5.
- [556] Ko, E. Y., Sabanegh, E. S., Jr. & Agarwal, A. (2014). Male infertility testing: reactive oxygen species and antioxidant capacity. *Fertil Steril* **102**, 1518-27.
- [557] Cruz, D. F., Lume, C., Silva, J. V., Nunes, A., Castro, I., Silva, R., Silva, V., Ferreira, R. & Fardilha, M. (2015). Oxidative stress markers: Can they be used to evaluate human sperm quality? *Turk J Urol* **41**, 198-207.
- [558] Agarwal, A. & Wang, S. M. (2017). Clinical Relevance of Oxidation-Reduction Potential in the Evaluation of Male Infertility. *Urology*.
- [559] Agarwal, A., Roychoudhury, S., Sharma, R., Gupta, S., Majzoub, A. & Sabanegh, E. (2017). Diagnostic application of oxidation-reduction potential assay for measurement of oxidative stress: clinical utility in male factor infertility. *Reprod Biomed Online* **34**, 48-57.
- [560] Bouziat, R., Hinterleitner, R., Brown, J. J., Stencel-Baerenwald, J. E., Ikizler, M., Mayassi, T., Meisel, M., Kim, S. M., Discepolo, V., Pruijssers, A. J., Ernest, J. D., Iskarpotyoti, J. A., Costes, L. M., Lawrence, I., Palanski, B. A., Varma, M., Zurenski, M. A., Khomandiak, S., McAllister, N., Aravamudhan, P., Boehme, K. W., Hu, F., Samsom, J. N., Reinecker, H. C., Kupfer, S. S., Guandalini, S., Semrad, C. E., Abadie, V., Khosla, C., Barreiro, L. B., Xavier, R. J., Ng, A., Dermody, T. S. & Jabri, B. (2017). Reovirus infection triggers inflammatory responses to dietary antigens and development of celiac disease. *Science* **356**, 44-50.
- [561] Verdu, E. F. & Caminero, A. (2017). How infection can incite sensitivity to food. *Science* **356**, 29-30.

- [562] Ludvigsson, J. F., Montgomery, S. M. & Ekblom, A. (2005). Celiac disease and risk of adverse fetal outcome: a population-based cohort study. *Gastroenterology* **129**, 454-63.
- [563] Wolf, H., Ilse, A., van Pampus, M. G., Sahebdi, S., Pena, S. & Von Blomberg, M. E. (2008). Celiac serology in women with severe pre-eclampsia or delivery of a small for gestational age neonate. *Int J Gynaecol Obstet* **103**, 175-7.
- [564] Bast, A., O'Bryan, T. & Bast, E. (2009). Celiac disease and reproductive health. *Practical Gastroenterol*, 10-21.
- [565] Özgör, B. & Selimoğlu, M. A. (2010). Coeliac disease and reproductive disorders. *Scand J Gastroenterol* **45**, 395-402.
- [566] Soni, S. & Badawy, S. Z. (2010). Celiac disease and its effect on human reproduction: a review. *J Reprod Med* **55**, 3-8.
- [567] Tersigni, C., Castellani, R., de Waure, C., Fattorossi, A., De Spirito, M., Gasbarrini, A., Scambia, G. & Di Simone, N. (2014). Celiac disease and reproductive disorders: meta-analysis of epidemiologic associations and potential pathogenic mechanisms. *Hum Reprod Update* **20**, 582-93.
- [568] Moleski, S. M., Lindenmeyer, C. C., Veloski, J. J., Miller, R. S., Miller, C. L., Kastenber, D. & DiMarino, A. J. (2015). Increased rates of pregnancy complications in women with celiac disease. *Ann Gastroenterol* **28**, 236-240.
- [569] Saccone, G., Berghella, V., Sarno, L., Maruotti, G. M., Cetin, I., Greco, L., Khashan, A. S., McCarthy, F., Martinelli, D., Fortunato, F. & Martinelli, P. (2016). Celiac disease and obstetric complications: a systematic review and metaanalysis. *Am J Obstet Gynecol* **214**, 225-34.
- [570] Byberg, K. K., Ogland, B., Eide, G. E. & Øymar, K. (2014). Birth after preeclamptic pregnancies: association with allergic sensitization and allergic rhinoconjunctivitis in late childhood; a historically matched cohort study. *BMC Pediatr* **14**, 101.
- [571] Liu, A. H. (2015). Revisiting the hygiene hypothesis for allergy and asthma. *J Allergy Clin Immunol* **136**, 860-5.
- [572] Stokholm, J., Sevelsted, A., Anderson, U. D. & Bisgaard, H. (2017). Preeclampsia Associates with Asthma, Allergy, and Eczema in Childhood. *Am J Respir Crit Care Med* **195**, 614-621.
- [573] Omer, S. B., Goodman, D., Steinhoff, M. C., Rochat, R., Klugman, K. P., Stoll, B. J. & Ramakrishnan, U. (2011). Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study. *PLoS Med* **8**, e1000441.
- [574] Adedinsaw, D. A., Noory, L., Bednarczyk, R. A., Steinhoff, M. C., Davis, R., Ogbuanu, C. & Omer, S. B. (2013). Impact of maternal characteristics on the effect of maternal influenza vaccination on fetal outcomes. *Vaccine* **31**, 5827-33.
- [575] Richards, J. L., Hansen, C., Bredfeldt, C., Bednarczyk, R. A., Steinhoff, M. C., Adjaye-Gbewonyo, D., Ault, K., Gallagher, M., Orenstein, W., Davis, R. L. & Omer, S. B. (2013). Neonatal outcomes after antenatal influenza immunization during the 2009 H1N1 influenza pandemic: impact on preterm birth, birth weight, and small for gestational age birth. *Clin Infect Dis* **56**, 1216-22.
- [576] Olsen, S. J., Mirza, S. A., Vonglokharn, P., Khanthamaly, V., Chitry, B., Pholsena, V., Chitranonh, V., Omer, S. B., Moen, A., Bresee, J. S., Corwin, A. & Xeuatvongsa, A. (2016). The Effect of Influenza Vaccination on Birth Outcomes in a Cohort of Pregnant Women in Lao PDR, 2014-2015. *Clin Infect Dis* **63**, 487-94.
- [577] Phadke, V. K., Steinhoff, M. C., Omer, S. B. & MacDonald, N. E. (2016). Maternal Influenza Immunization and Adverse Birth Outcomes: Using Data and Practice to Inform Theory and Research Design. *Am J Epidemiol* **184**, 789-792.
- [578] Leslie, M. (2017). Can flu shots help women get pregnant? *Science* **355**, 1247-1248.
- [579] Nordin, J. D., Kharbanda, E. O., Vazquez Benitez, G., Lipkind, H., Vellozzi, C., Destefano, F. & Vaccine Safety, D. (2014). Maternal influenza vaccine and risks for preterm or small for gestational age birth. *J Pediatr* **164**, 1051-1057 e2.
- [580] Bratton, K. N., Wardle, M. T., Orenstein, W. A. & Omer, S. B. (2015). Maternal influenza immunization and birth outcomes of stillbirth and spontaneous abortion: a systematic review and meta-analysis. *Clin Infect Dis* **60**, e11-9.
- [581] Coenders, A., Koopmans, N. K., Broekhuijsen, K., Groen, H., Karstenberg-Kramer, J. M. A., van Goor, K., Groenewout, M., van Loon, A. J., Faas, M. M. & van Pampus, M. G. (2015).

- Adjuvanted vaccines in pregnancy: no evidence for effect of the adjuvanted H1N1/09 vaccination on occurrence of preeclampsia or intra-uterine growth restriction. *Eur J Obstet Gynecol Reprod Biol* **187**, 14-9.
- [582] Munoz, F. M., Greisinger, A. J., Wehmanen, O. A., Mouzoon, M. E., Hoyle, J. C., Smith, F. A. & Glezen, W. P. (2005). Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol* **192**, 1098-106.
- [583] Mak, T. K., Mangtani, P., Leese, J., Watson, J. M. & Pfeifer, D. (2008). Influenza vaccination in pregnancy: current evidence and selected national policies. *Lancet Infect Dis* **8**, 44-52.
- [584] Tamma, P. D., Ault, K. A., del Rio, C., Steinhoff, M. C., Halsey, N. A. & Omer, S. B. (2009). Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol* **201**, 547-52.
- [585] Yamaguchi, K., Hisano, M., Isojima, S., Irie, S., Arata, N., Watanabe, N., Kubo, T., Kato, T. & Murashima, A. (2009). Relationship of Th1/Th2 cell balance with the immune response to influenza vaccine during pregnancy. *J Med Virol* **81**, 1923-8.
- [586] Bednarczyk, R. A., Adjaye-Gbewonyo, D. & Omer, S. B. (2012). Safety of influenza immunization during pregnancy for the fetus and the neonate. *Am J Obstet Gynecol* **207**, S38-46.
- [587] Jamieson, D. J., Kissin, D. M., Bridges, C. B. & Rasmussen, S. A. (2012). Benefits of influenza vaccination during pregnancy for pregnant women. *Am J Obstet Gynecol* **207**, S17-20.
- [588] Kharbanda, E. O., Vazquez-Benitez, G., Shi, W. X., Lipkind, H., Naleway, A., Molitor, B., Kuckler, L., Olsen, A. & Nordin, J. D. (2012). Assessing the safety of influenza immunization during pregnancy: the Vaccine Safety Datalink. *Am J Obstet Gynecol* **207**, S47-51.
- [589] Moro, P. L., Tepper, N. K., Grohskopf, L. A., Vellozzi, C. & Broder, K. (2012). Safety of seasonal influenza and influenza A (H1N1) 2009 monovalent vaccines in pregnancy. *Expert Rev Vaccines* **11**, 911-21.
- [590] Pasternak, B., Svanström, H., Mølgaard-Nielsen, D., Krause, T. G., Emborg, H. D., Melbye, M. & Hviid, A. (2012). Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: cohort study in Denmark. *BMJ* **344**, e2794.
- [591] Pasternak, B., Svanström, H., Mølgaard-Nielsen, D., Krause, T. G., Emborg, H. D., Melbye, M. & Hviid, A. (2012). Risk of adverse fetal outcomes following administration of a pandemic influenza A(H1N1) vaccine during pregnancy. *JAMA* **308**, 165-74.
- [592] Beau, A. B., Hurault-Delarue, C., Vidal, S., Guitard, C., Vayssière, C., Petiot, D., Montastruc, J. L., Damase-Michel, C. & Lacroix, I. (2014). Pandemic A/H1N1 influenza vaccination during pregnancy: a comparative study using the EFEMERIS database. *Vaccine* **32**, 1254-8.
- [593] Keller-Stanislawski, B., Englund, J. A., Kang, G., Mangtani, P., Neuzil, K., Nohynek, H., Pless, R., Lambach, P. & Zuber, P. (2014). Safety of immunization during pregnancy: a review of the evidence of selected inactivated and live attenuated vaccines. *Vaccine* **32**, 7057-64.
- [594] Naleway, A. L., Irving, S. A., Henninger, M. L., Li, D. K., Shifflett, P., Ball, S., Williams, J. L., Cragan, J., Gee, J., Thompson, M. G., Vaccine Safety Datalink & Pregnancy & Influenza Project Workgroup. (2014). Safety of influenza vaccination during pregnancy: a review of subsequent maternal obstetric events and findings from two recent cohort studies. *Vaccine* **32**, 3122-7.
- [595] Vaughn, D. W., Seifert, H., Hepburn, A., Dewe, W., Li, P., Drame, M., Cohet, C., Innis, B. L. & Fries, L. F. (2014). Safety of AS03-adjuvanted inactivated split virion A(H1N1)pdm09 and H5N1 influenza virus vaccines administered to adults: pooled analysis of 28 clinical trials. *Hum Vaccin Immunother* **10**, 2942-57.
- [596] Baum, U., Leino, T., Gissler, M., Kilpi, T. & Jokinen, J. (2015). Perinatal survival and health after maternal influenza A(H1N1)pdm09 vaccination: A cohort study of pregnancies stratified by trimester of vaccination. *Vaccine* **33**, 4850-7.
- [597] Fabiani, M., Bella, A., Rota, M. C., Clagnan, E., Gallo, T., D'Amato, M., Pezzotti, P., Ferrara, L., Demicheli, V., Martinelli, D., Prato, R. & Rizzo, C. (2015). A/H1N1 pandemic influenza vaccination: A retrospective evaluation of adverse maternal, fetal and neonatal outcomes in a cohort of pregnant women in Italy. *Vaccine* **33**, 2240-7.

- [598] Fell, D. B., Platt, R. W., Lanes, A., Wilson, K., Kaufman, J. S., Basso, O. & Buckeridge, D. (2015). Fetal death and preterm birth associated with maternal influenza vaccination: systematic review. *BJOG* **122**, 17-26.
- [599] Ludvigsson, J. F., Ström, P., Lundholm, C., Cnattingius, S., Ekbom, A., Örtqvist, Å., Feltelius, N., Granath, F. & Stephansson, O. (2015). Maternal vaccination against H1N1 influenza and offspring mortality: population based cohort study and sibling design. *BMJ* **351**, h5585.
- [600] Savitz, D. A., Fell, D. B., Ortiz, J. R. & Bhat, N. (2015). Does influenza vaccination improve pregnancy outcome? Methodological issues and research needs. *Vaccine* **33**, 6430-5.
- [601] Walls, T., Graham, P., Petousis-Harris, H., Hill, L. & Austin, N. (2016). Infant outcomes after exposure to Tdap vaccine in pregnancy: an observational study. *BMJ Open* **6**, e009536.
- [602] Donegan, K., King, B. & Bryan, P. (2014). Safety of pertussis vaccination in pregnant women in UK: observational study. *BMJ* **349**, g4219.
- [603] Kharbanda, E. O., Vazquez-Benitez, G., Lipkind, H. S., Klein, N. P., Cheetham, T. C., Naleway, A. L., Lee, G. M., Hambidge, S., Jackson, M. L., Omer, S. B., McCarthy, N. & Nordin, J. D. (2016). Maternal Tdap vaccination: Coverage and acute safety outcomes in the vaccine safety datalink, 2007-2013. *Vaccine* **34**, 968-73.
- [604] Petousis-Harris, H., Walls, T., Watson, D., Paynter, J., Graham, P. & Turner, N. (2016). Safety of Tdap vaccine in pregnant women: an observational study. *BMJ Open* **6**, e010911.
- [605] Wheeler, C. M., Skinner, S. R., Del Rosario-Raymundo, M. R., Garland, S. M., Chatterjee, A., Lazcano-Ponce, E., Salmerón, J., McNeil, S., Stapleton, J. T., Bouchard, C., Martens, M. G., Money, D. M., Quek, S. C., Romanowski, B., Vallejos, C. S., Ter Harmsel, B., Prilepskaya, V., Fong, K. L., Kitchener, H., Minkina, G., Lim, Y. K., Stoney, T., Chakhtoura, N., Cruickshank, M. E., Savicheva, A., da Silva, D. P., Ferguson, M., Molijn, A. C., Quint, W. G. V., Hardt, K., Descamps, D., Suryakiran, P. V., Karkada, N., Geeraerts, B., Dubin, G., Struyf, F. & Viviane Study Group. (2016). Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. *Lancet Infect Dis* **16**, 1154-68.
- [606] Raj, R. S., Bonney, E. A. & Phillippe, M. (2014). Influenza, immune system, and pregnancy. *Reprod Sci* **21**, 1434-51.
- [607] Staff, A. C., Benton, S. J., von Dadelszen, P., Roberts, J. M., Taylor, R. N., Powers, R. W., Charnock-Jones, D. S. & Redman, C. W. G. (2013). Redefining preeclampsia using placenta-derived biomarkers. *Hypertension* **61**, 932-42.
- [608] Scheminske, M., Henninger, M., Irving, S. A., Thompson, M., Williams, J., Shifflett, P., Ball, S. W., Avalos, L. A., Naleway, A. L. & Pregnancy & Influenza Project Workgroup. (2015). The association between influenza vaccination and other preventative health behaviors in a cohort of pregnant women. *Health Educ Behav* **42**, 402-8.
- [609] Steinhoff, M. C., Omer, S. B., Roy, E., El Arifeen, S., Raqib, R., Dodd, C., Breiman, R. F. & Zaman, K. (2012). Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial. *CMAJ* **184**, 645-53.
- [610] Porter, T. F., LaCoursiere, Y. & Scott, J. R. (2006). Immunotherapy for recurrent miscarriage. *Cochrane Database Syst Rev*, CD000112.
- [611] Wong, L. F., Porter, T. F. & Scott, J. R. (2014). Immunotherapy for recurrent miscarriage. *Cochrane Database Syst Rev*, CD000112.
- [612] Jørgensen, K. T., Pedersen, B. V., Jacobsen, S., Biggar, R. J. & Frisch, M. (2010). National cohort study of reproductive risk factors for rheumatoid arthritis in Denmark: a role for hyperemesis, gestational hypertension and pre-eclampsia? *Ann Rheum Dis* **69**, 358-63.
- [613] Ebringer, A., Rashid, T. & Wilson, C. (2010). Rheumatoid arthritis, Proteus, anti-CCP antibodies and Karl Popper. *Autoimmun Rev* **9**, 216-23.
- [614] Ebringer, A. (2012). *Rheumatoid arthritis and Proteus*. Springer, London.
- [615] Ebringer, A. & Rashid, T. (2014). Rheumatoid arthritis is caused by a *Proteus* urinary tract infection. *APMIS* **122**, 363-8.
- [616] Pretorius, E., Akeredolu, O.-O., Soma, P. & Kell, D. B. (2017). Major involvement of bacterial components in rheumatoid arthritis and its accompanying oxidative stress, systemic inflammation and hypercoagulability. *Exp Biol Med* **242**, 355-373.
- [617] Wang, G., Li, X. & Wang, Z. (2016). APD3: the antimicrobial peptide database as a tool for research and education. *Nucleic Acids Res* **44**, D1087-93.

- [618] Zasloff, M. (2002). Antimicrobial peptides of multicellular organisms. *Nature* **415**, 389-95.
- [619] Auvynet, C. & Rosenstein, Y. (2009). Multifunctional host defense peptides: antimicrobial peptides, the small yet big players in innate and adaptive immunity. *FEBS J* **276**, 6497-508.
- [620] Gustafsson, A., Olin, A. I. & Ljunggren, L. (2010). LPS interactions with immobilized and soluble antimicrobial peptides. *Scand J Clin Lab Invest* **70**, 194-200.
- [621] Lee, S. H., Jun, H. K., Lee, H. R., Chung, C. P. & Choi, B. K. (2010). Antibacterial and lipopolysaccharide (LPS)-neutralising activity of human cationic antimicrobial peptides against periodontopathogens. *Int J Antimicrob Agents* **35**, 138-45.
- [622] Kościuczuk, E. M., Lisowski, P., Jarczak, J., Strzałkowska, N., Jóźwik, A., Horbańczuk, J., Krzyzewski, J., Zwierzchowski, L. & Bagnicka, E. (2012). Cathelicidins: family of antimicrobial peptides. A review. *Mol Biol Rep* **39**, 10957-70.
- [623] Seo, M. D., Won, H. S., Kim, J. H., Mishig-Ochir, T. & Lee, B. J. (2012). Antimicrobial peptides for therapeutic applications: a review. *Molecules* **17**, 12276-86.
- [624] Zhao, J., Zhao, C., Liang, G., Zhang, M. & Zheng, J. (2013). Engineering antimicrobial peptides with improved antimicrobial and hemolytic activities. *J Chem Inf Model* **53**, 3280-96.
- [625] Ashby, M., Petkova, A. & Hilpert, K. (2014). Cationic antimicrobial peptides as potential new therapeutic agents in neonates and children: a review. *Curr Opin Infect Dis* **27**, 258-67.
- [626] Waghu, F. H., Gopi, L., Barai, R. S., Ramteke, P., Nizami, B. & Idicula-Thomas, S. (2014). CAMP: Collection of sequences and structures of antimicrobial peptides. *Nucleic Acids Res* **42**, D1154-8.
- [627] Wang, G. (2014). Human antimicrobial peptides and proteins. *Pharmaceuticals (Basel)* **7**, 545-94.
- [628] Kido, E. A., Pandolfi, V., Houllou-Kido, L. M., Andrade, P. P., Marcelino, F. C., Nepomuceno, A. L., Abdelnoor, R. V., Burnquist, W. L. & Benko-Iseppon, A. M. (2010). Plant antimicrobial peptides: an overview of SuperSAGE transcriptional profile and a functional review. *Curr Protein Pept Sci* **11**, 220-30.
- [629] Li, W., Tailhades, J., O'Brien-Simpson, N. M., Separovic, F., Otvos, L., Jr., Hossain, M. A. & Wade, J. D. (2014). Proline-rich antimicrobial peptides: potential therapeutics against antibiotic-resistant bacteria. *Amino Acids* **46**, 2287-94.
- [630] Kosikowska, P. & Lesner, A. (2016). Antimicrobial peptides (AMPs) as drug candidates: a patent review (2003-2015). *Expert Opin Ther Pat* **26**, 689-702.
- [631] Kang, H. K., Kim, C., Seo, C. H. & Park, Y. (2017). The therapeutic applications of antimicrobial peptides (AMPs): a patent review. *J Microbiol* **55**, 1-12.
- [632] Yoshio, H., Tollin, M., Gudmundsson, G. H., Lagercrantz, H., Jornvall, H., Marchini, G. & Agerberth, B. (2003). Antimicrobial polypeptides of human vernix caseosa and amniotic fluid: implications for newborn innate defense. *Pediatr Res* **53**, 211-6.
- [633] Frew, L. & Stock, S. J. (2011). Antimicrobial peptides and pregnancy. *Reproduction* **141**, 725-35.
- [634] Kai-Larsen, Y., Gudmundsson, G. H. & Agerberth, B. (2014). A review of the innate immune defence of the human foetus and newborn, with the emphasis on antimicrobial peptides. *Acta Paediatr* **103**, 1000-8.
- [635] Tribe, R. M. (2015). Small Peptides with a Big Role: Antimicrobial Peptides in the Pregnant Female Reproductive Tract. *Am J Reprod Immunol* **74**, 123-5.
- [636] Yarbrough, V. L., Winkle, S. & Herbst-Kralovetz, M. M. (2015). Antimicrobial peptides in the female reproductive tract: a critical component of the mucosal immune barrier with physiological and clinical implications. *Hum Reprod Update* **21**, 353-77.
- [637] Zairi, A., Tangy, F., Bouassida, K. & Hani, K. (2009). Dermaseptins and magainins: antimicrobial peptides from frogs' skin-new sources for a promising spermicides microbicides-a mini review. *J Biomed Biotechnol* **2009**, 452567.
- [638] Yedery, R. D. & Reddy, K. V. R. (2005). Antimicrobial peptides as microbicidal contraceptives: prophecies for prophylactics--a mini review. *Eur J Contracept Reprod Health Care* **10**, 32-42.
- [639] Bussalleu, E., Sancho, S., Briz, M. D., Yeste, M. & Bonet, S. (2017). Do antimicrobial peptides PR-39, PMAP-36 and PMAP-37 have any effect on bacterial growth and quality of liquid-stored boar semen? *Theriogenology* **89**, 235-243.

- [640] Schulze, M., Dathe, M., Waberski, D. & Müller, K. (2016). Liquid storage of boar semen: Current and future perspectives on the use of cationic antimicrobial peptides to replace antibiotics in semen extenders. *Theriogenology* **85**, 39-46.
- [641] Schulze, M., Grobbel, M., Müller, K., Junkes, C., Dathe, M., Rüdiger, K. & Jung, M. (2015). Challenges and Limits Using Antimicrobial Peptides in Boar Semen Preservation. *Reprod Domest Anim* **50 Suppl 2**, 5-10.
- [642] Schulze, M., Junkes, C., Mueller, P., Speck, S., Ruediger, K., Dathe, M. & Mueller, K. (2014). Effects of cationic antimicrobial peptides on liquid-preserved boar spermatozoa. *PLoS One* **9**, e100490.
- [643] Speck, S., Courtiol, A., Junkes, C., Dathe, M., Müller, K. & Schulze, M. (2014). Cationic synthetic peptides: assessment of their antimicrobial potency in liquid preserved boar semen. *PLoS One* **9**, e105949.
- [644] Easterhoff, D., Ontiveros, F., Brooks, L. R., Kim, Y., Ross, B., Silva, J. N., Olsen, J. S., Feng, C., Hardy, D. J., Dunman, P. M. & Dewhurst, S. (2013). Semen-derived enhancer of viral infection (SEVI) binds bacteria, enhances bacterial phagocytosis by macrophages, and can protect against vaginal infection by a sexually transmitted bacterial pathogen. *Antimicrob Agents Chemother* **57**, 2443-50.
- [645] Zhao, H., Lee, W. H., Shen, J. H., Li, H. & Zhang, Y. (2008). Identification of novel semenogelin I-derived antimicrobial peptide from liquefied human seminal plasma. *Peptides* **29**, 505-11.
- [646] Edström, A. M. L., Malm, J., Frohm, B., Martellini, J. A., Giwerzman, A., Mörgelin, M., Cole, A. M. & Sørensen, O. E. (2008). The major bactericidal activity of human seminal plasma is zinc-dependent and derived from fragmentation of the semenogelins. *J Immunol* **181**, 3413-21.
- [647] Yenugu, S., Hamil, K. G., Birse, C. E., Ruben, S. M., French, F. S. & Hall, S. H. (2003). Antibacterial properties of the sperm-binding proteins and peptides of human epididymis 2 (HE2) family; salt sensitivity, structural dependence and their interaction with outer and cytoplasmic membranes of *Escherichia coli*. *Biochem J* **372**, 473-83.
- [648] Avellar, M. C. W., Honda, L., Hamil, K. G., Yenugu, S., Grossman, G., Petrusz, P., French, F. S. & Hall, S. H. (2004). Differential expression and antibacterial activity of epididymis protein 2 isoforms in the male reproductive tract of human and rhesus monkey (*Macaca mulatta*). *Biol Reprod* **71**, 1453-60.
- [649] Sørensen, O. E., Gram, L., Johnsen, A. H., Andersson, E., Bangsbøll, S., Tjabringa, G. S., Hiemstra, P. S., Malm, J., Egesten, A. & Borregaard, N. (2003). Processing of seminal plasma hCAP-18 to ALL-38 by gastricsin: a novel mechanism of generating antimicrobial peptides in vagina. *J Biol Chem* **278**, 28540-6.
- [650] Williams, R. J. (1956). *Biochemical Individuality*. John Wiley, New York.
- [651] Ayres, J. S., Freitag, N. & Schneider, D. S. (2008). Identification of *Drosophila* mutants altering defense of and endurance to *Listeria monocytogenes* infection. *Genetics* **178**, 1807-15.
- [652] Schneider, D. S. & Ayres, J. S. (2008). Two ways to survive infection: what resistance and tolerance can teach us about treating infectious diseases. *Nat Rev Immunol* **8**, 889-95.
- [653] Råberg, L., Graham, A. L. & Read, A. F. (2009). Decomposing health: tolerance and resistance to parasites in animals. *Philos Trans R Soc Lond B Biol Sci* **364**, 37-49.
- [654] Ayres, J. S. & Schneider, D. S. (2012). Tolerance of infections. *Annu Rev Immunol* **30**, 271-94.
- [655] Medzhitov, R., Schneider, D. S. & Soares, M. P. (2012). Disease tolerance as a defense strategy. *Science* **335**, 936-41.
- [656] Råberg, L. (2014). How to live with the enemy: understanding tolerance to parasites. *PLoS Biol* **12**, e1001989.
- [657] Palaferri Schieber, A. M., Lee, Y. M., Chang, M. W., Leblanc, M., Collins, B., Downes, M., Evans, R. M. & Ayres, J. S. (2015). Disease tolerance mediated by microbiome *E. coli* involves inflammasome and IGF-1 signaling. *Science* **350**, 558-63.
- [658] Kogut, M. H. & Arsenault, R. J. (2017). Immunometabolic Phenotype Alterations Associated with the Induction of Disease Tolerance and Persistent Asymptomatic Infection of *Salmonella* in the Chicken Intestine. *Front Immunol* **8**, 372.

- [659] Meunier, I., Kaufmann, E., Downey, J. & Divangahi, M. (2017). Unravelling the networks dictating host resistance versus tolerance during pulmonary infections. *Cell Tissue Res* **367**, 525-536.
- [660] Gluckman, P., Beedle, A. & Hanson, M. (2009). *Principles of evolutionary medicine*. Oxford University Press, Oxford.
- [661] Longo, V. D. & Finch, C. E. (2003). Evolutionary medicine: from dwarf model systems to healthy centenarians? *Science* **299**, 1342-6.
- [662] Rühli, F. J. & Henneberg, M. (2013). New perspectives on evolutionary medicine: the relevance of microevolution for human health and disease. *BMC Med* **11**, 115.
- [663] Svensson, E. I. & Råberg, L. (2010). Resistance and tolerance in animal enemy-victim coevolution. *Trends Ecol Evol* **25**, 267-74.
- [664] Ayres, J. S. (2016). Cooperative Microbial Tolerance Behaviors in Host-Microbiota Mutualism. *Cell* **165**, 1323-31.
- [665] Ayres, J. S. (2017). Microbes Dress for Success: Tolerance or Resistance? *Trends Microbiol* **25**, 1-3.
- [666] Rangan, K. J., Pedicord, V. A., Wang, Y. C., Kim, B., Lu, Y., Shaham, S., Mucida, D. & Hang, H. C. (2016). A secreted bacterial peptidoglycan hydrolase enhances tolerance to enteric pathogens. *Science* **353**, 1434-1437.
- [667] Than, N. G., Balogh, A., Romero, R., Kárpáti, É., Erez, O., Szilágyi, A., Kovalszky, I., Sammar, M., Gizurarson, S., Matkó, J., Závodszy, P., Papp, Z. & Meiri, H. (2014). Placental Protein 13 (PP13) - A Placental Immunoregulatory Galectin Protecting Pregnancy. *Front Immunol* **5**, 348.
- [668] Seremak-Mrozikiewicz, A. (2008). Genetics of preeclampsia – current concepts. *Arch Perinatal Med* **14**, 9-11.
- [669] Bohn, H., Kraus, W. & Winckler, W. (1983). Purification and characterization of two new soluble placental tissue proteins (PP13 and PP17). *Oncodev Biol Med* **4**, 343-50.
- [670] Visegrády, B., Than, N. G., Kilár, F., Sümegi, B., Than, G. N. & Bohn, H. (2001). Homology modelling and molecular dynamics studies of human placental tissue protein 13 (galectin-13). *Protein Eng* **14**, 875-80.
- [671] Than, N. G., Pick, E., Bellyei, S., Szigeti, A., Burger, O., Berente, Z., Janaky, T., Boronkai, A., Kliman, H., Meiri, H., Bohn, H., Than, G. N. & Sumegi, B. (2004). Functional analyses of placental protein 13/galectin-13. *Eur J Biochem* **271**, 1065-78.
- [672] Than, N. G., Sumegi, B., Than, G. N., Berente, Z. & Bohn, H. (1999). Isolation and sequence analysis of a cDNA encoding human placental tissue protein 13 (PP13), a new lysophospholipase, homologue of human eosinophil Charcot-Leyden Crystal protein. *Placenta* **20**, 703-10.
- [673] Romero, R., Kusanovic, J. P., Than, N. G., Erez, O., Gotsch, F., Espinoza, J., Edwin, S., Chafetz, I., Gomez, R., Nien, J. K., Sammar, M., Pineles, B., Hassan, S. S., Meiri, H., Tal, Y., Kuhnreich, I., Papp, Z. & Cuckle, H. S. (2008). First-trimester maternal serum PP13 in the risk assessment for preeclampsia. *Am J Obstet Gynecol* **199**, 122 e1-122 e11.
- [674] Cowans, N. J., Stamatopoulou, A., Khalil, A. & Spencer, K. (2011). PP13 as a marker of pre-eclampsia: A two platform comparison study. *Placenta* **32 Suppl**, S37-41.
- [675] De Muro, P., Capobianco, G., Lepedda, A. J., Nieddu, G., Formato, M., Tram, N. H. Q., Idini, M., Dessole, F. & Dessole, S. (2016). Plasma PP13 and urinary GAGs/PGs as early markers of pre-eclampsia. *Arch Gynecol Obstet* **294**, 959-965.
- [676] Than, N. G., Abdul Rahman, O., Magenheimer, R., Nagy, B., Fule, T., Hargitai, B., Sammar, M., Hupuczi, P., Tarca, A. L., Szabo, G., Kovalszky, I., Meiri, H., Sziller, I., Rigo, J., Jr., Romero, R. & Papp, Z. (2008). Placental protein 13 (galectin-13) has decreased placental expression but increased shedding and maternal serum concentrations in patients presenting with preterm pre-eclampsia and HELLP syndrome. *Virchows Arch* **453**, 387-400.
- [677] Bruiners, N., Bosman, M., Postma, A., Gebhardt, S., Rebello, G., Sammar, M., Meiri, H. & Hillermann, R. (2007). Promoter variant-98A-C of the LGALS13 gene and pre-eclampsia. *Proceedings of the 8th World Congress of Perinatal Medicine*, 371-374.
- [678] Than, N. G., Erez, O., Wildman, D. E., Tarca, A. L., Edwin, S. S., Abbas, A., Hotra, J., Kusanovic, J. P., Gotsch, F., Hassan, S. S., Espinoza, J., Papp, Z. & Romero, R. (2008). Severe preeclampsia is characterized by increased placental expression of galectin-1. *J Matern Fetal Neonatal Med* **21**, 429-42.

- [679] Barrett, T., Wilhite, S. E., Ledoux, P., Evangelista, C., Kim, I. F., Tomashevsky, M., Marshall, K. A., Phillippy, K. H., Sherman, P. M., Holko, M., Yefanov, A., Lee, H., Zhang, N., Robertson, C. L., Serova, N., Davis, S. & Soboleva, A. (2013). NCBI GEO: archive for functional genomics data sets--update. *Nucleic Acids Res* **41**, D991-5.
- [680] Vasta, G. R. (2009). Roles of galectins in infection. *Nat Rev Microbiol* **7**, 424-38.
- [681] Poltorak, A., He, X. L., Smirnova, I., Liu, M. Y., Van Huffel, C., Du, X., Birdwell, D., Alejos, E., Silva, M., Galanos, C., Freudenberg, M., Ricciardi-Castagnoli, P., Layton, B. & Beutler, B. (1998). Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: Mutations in Tlr4 gene. *Science* **282**, 2085-2088.
- [682] Hoshino, K., Takeuchi, O., Kawai, T., Sanjo, H., Ogawa, T., Takeda, Y., Takeda, K. & Akira, S. (1999). Toll-like receptor 4 (TLR4)-deficient mice are hyporesponsive to lipopolysaccharide: Evidence for TLR4 as the Lps gene product. *J Immunol* **162**, 3749-3752.
- [683] Lien, E., Means, T. K., Heine, H., Yoshimura, A., Kusumoto, S., Fukase, K., Fenton, M. J., Oikawa, M., Qureshi, N., Monks, B., Finberg, R. W., Ingalls, R. R. & Golenbock, D. T. (2000). Toll-like receptor 4 imparts ligand-specific recognition of bacterial lipopolysaccharide. *J Clin Invest* **105**, 497-504.
- [684] Schwandner, R., Dziarski, R., Wesche, H., Rothe, M. & Kirschning, C. J. (1999). Peptidoglycan- and lipoteichoic acid-induced cell activation is mediated by toll-like receptor 2. *J Biol Chem* **274**, 17406-9.
- [685] Underhill, D. M., Ozinsky, A., Hajjar, A. M., Stevens, A., Wilson, C. B., Bassetti, M. & Aderem, A. (1999). The Toll-like receptor 2 is recruited to macrophage phagosomes and discriminates between pathogens. *Nature* **401**, 811-5.
- [686] Ishii, K. J. & Akira, S. (2004). Toll-like Receptors and Sepsis. *Curr Infect Dis Rep* **6**, 361-366.
- [687] Zähringer, U., Lindner, B., Inamura, S., Heine, H. & Alexander, C. (2008). TLR2 - promiscuous or specific? A critical re-evaluation of a receptor expressing apparent broad specificity. *Immunobiology* **213**, 205-224.
- [688] Kawai, T. & Akira, S. (2011). Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. *Immunity* **34**, 637-650.
- [689] Kumar, H., Kawai, T. & Akira, S. (2011). Pathogen recognition by the innate immune system. *Int Rev Immunol* **30**, 16-34.
- [690] Oliveira-Nascimento, L., Massari, P. & Wetzler, L. M. (2012). The Role of TLR2 in Infection and Immunity. *Front Immunol* **3**, 79.
- [691] Kumar, S., Ingle, H., Prasad, D. V. & Kumar, H. (2013). Recognition of bacterial infection by innate immune sensors. *Crit Rev Microbiol* **39**, 229-46.
- [692] Alexander, S. P. A., Benson, H. E., Faccenda, E., Pawson, A. J., Sharman, J. L., Spedding, M., Peters, J. A., Harman, A. J. & CGTP Collaborators. (2013). The Concise Guide to PHARMACOLOGY 2013/14: catalytic receptors. *Br J Pharmacol* **170**, 1676-705.
- [693] Liu, Y., Yin, H., Zhao, M. & Lu, Q. (2014). TLR2 and TLR4 in autoimmune diseases: a comprehensive review. *Clin Rev Allergy Immunol* **47**, 136-47.
- [694] Mukherjee, S., Karmakar, S. & Babu, S. P. (2016). TLR2 and TLR4 mediated host immune responses in major infectious diseases: a review. *Braz J Infect Dis* **20**, 193-204.
- [695] Jiménez-Dalmaroni, M. J., Gerswhin, M. E. & Adamopoulos, I. E. (2016). The critical role of toll-like receptors--From microbial recognition to autoimmunity: A comprehensive review. *Autoimmun Rev* **15**, 1-8.
- [696] Tinsley, J. H., Chiasson, V. L., Mahajan, A., Young, K. J. & Mitchell, B. M. (2009). Toll-like receptor 3 activation during pregnancy elicits preeclampsia-like symptoms in rats. *Am J Hypertens* **22**, 1314-9.
- [697] Girling, J. E. & Hedger, M. P. (2007). Toll-like receptors in the gonads and reproductive tract: emerging roles in reproductive physiology and pathology. *Immunol Cell Biol* **85**, 481-9.
- [698] van Rijn, B. B., Franx, A., Steegers, E. A. P., de Groot, C. J. M., Bertina, R. M., Pasterkamp, G., Voorbij, H. A. M., Bruinse, H. W. & Roest, M. (2008). Maternal TLR4 and NOD2 gene variants, pro-inflammatory phenotype and susceptibility to early-onset preeclampsia and HELLP syndrome. *PLoS One* **3**, e1865.
- [699] Riley, J. K. & Nelson, D. M. (2010). Toll-like receptors in pregnancy disorders and placental dysfunction. *Clin Rev Allergy Immunol* **39**, 185-93.

- [700] Pineda, A., Verdin-Terán, S. L., Camacho, A. & Moreno-Fierros, L. (2011). Expression of toll-like receptor TLR-2, TLR-3, TLR-4 and TLR-9 is increased in placentas from patients with preeclampsia. *Arch Med Res* **42**, 382-91.
- [701] Panda, B., Panda, A., Ueda, I., Abrahams, V. M., Norwitz, E. R., Stanic, A. K., Young, B. C., Ecker, J. L., Altfeld, M., Shaw, A. C. & Rueda, B. R. (2012). Dendritic cells in the circulation of women with preeclampsia demonstrate a pro-inflammatory bias secondary to dysregulation of TLR receptors. *J Reprod Immunol* **94**, 210-5.
- [702] Zhang, L. & Yang, H. (2012). Expression and localization of TLR4 and its negative regulator Tollip in the placenta of early-onset and late-onset preeclampsia. *Hypertens Pregnancy* **31**, 218-27.
- [703] Amirchaghmaghi, E., Taghavi, S. A., Shapouri, F., Saeidi, S., Rezaei, A. & Aflatoonian, R. (2013). The role of toll like receptors in pregnancy. *Int J Fertil Steril* **7**, 147-54.
- [704] Zhu, Y., Wu, M., Wu, C. Y. & Xia, G. Q. (2013). Role of progesterone in TLR4-MyD88-dependent signaling pathway in pre-eclampsia. *J Huazhong Univ Sci Technolog Med Sci* **33**, 730-4.
- [705] Koga, K., Izumi, G., Mor, G., Fujii, T. & Osuga, Y. (2014). Toll-like receptors at the maternal-fetal interface in normal pregnancy and pregnancy complications. *Am J Reprod Immunol* **72**, 192-205.
- [706] Xue, P. P., Zheng, M. M., Gong, P., Lin, C. M., Zhou, J. J., Li, Y. J., Shen, L., Diao, Z. Y., Yan, G. J., Sun, H. X. & Hu, Y. L. (2015). Single Administration of Ultra-Low-Dose Lipopolysaccharide in Rat Early Pregnancy Induces TLR4 Activation in the Placenta Contributing to Preeclampsia. *Plos One* **10**.
- [707] Kulikova, G. V., Nizyaeva, N. V., Nagovitsina, M. N., Lyapin, V. M., Loginova, N. S., Kan, N. E., Tyutyunnik, V. L., Tyutyunnik, N. V. & Schegolev, A. I. (2016). Specific Features of TLR4 Expression in Structural Elements of Placenta in Patients with Preeclampsia. *Bull Exp Biol Med* **160**, 718-21.
- [708] Gong, P., Liu, M., Hong, G., Li, Y., Xue, P., Zheng, M., Wu, M., Shen, L., Yang, M., Diao, Z. & Hu, Y. (2016). Curcumin improves LPS-induced preeclampsia-like phenotype in rat by inhibiting the TLR4 signaling pathway. *Placenta* **41**, 45-52.
- [709] Faas, M. M., Schuiling, G. A., Baller, J. F., Visscher, C. A. & Bakker, W. W. (1994). A new animal model for human preeclampsia: ultra-low-dose endotoxin infusion in pregnant rats. *Am J Obstet Gynecol* **171**, 158-64.
- [710] Fujita, Y., Mihara, T., Okazaki, T., Shitanaka, M., Kushino, R., Ikeda, C., Negishi, H., Liu, Z., Richards, J. S. & Shimada, M. (2011). Toll-like receptors (TLR) 2 and 4 on human sperm recognize bacterial endotoxins and mediate apoptosis. *Hum Reprod* **26**, 2799-806.
- [711] Li, N., Wang, T. & Han, D. (2012). Structural, cellular and molecular aspects of immune privilege in the testis. *Front Immunol* **3**, 152.
- [712] Saeidi, S., Shapouri, F., Amirchaghmaghi, E., Hoseinifar, H., Sabbaghian, M., Sadighi Gilani, M. A., Pacey, A. A. & Aflatoonian, R. (2014). Sperm protection in the male reproductive tract by Toll-like receptors. *Andrologia* **46**, 784-90.
- [713] Hagan, S., Khurana, N., Chandra, S., Abdel-Mageed, A. B., Mondal, D., Hellstrom, W. J. & Sikka, S. C. (2015). Differential expression of novel biomarkers (TLR-2, TLR-4, COX-2, and Nrf-2) of inflammation and oxidative stress in semen of leukocytospermia patients. *Andrology* **3**, 848-55.
- [714] Pretorius, E., Bester, J. & Kell, D. B. (2016). A bacterial component to Alzheimer-type dementia seen via a systems biology approach that links iron dysregulation and inflammagen shedding to disease *J Alzheimers Dis* **53**, 1237-1256.
- [715] Kell, D. B. & Pretorius, E. (2017). To what extent are the terminal stages of sepsis, septic shock, SIRS, and multiple organ dysfunction syndrome actually driven by a toxic prion/amyloid form of fibrin? *Semin Thromb Hemost*, in press.
- [716] Pretorius, E., Mbotwe, S. & Kell, D. B. (2017). Lipopolysaccharide-binding protein (LBP) reverses the amyloid state of fibrin seen in plasma of type 2 diabetics with cardiovascular comorbidities. *Sci Rep* **7**, 9680.
- [717] Cervera, R. & Balasch, J. (2008). Bidirectional effects on autoimmunity and reproduction. *Hum Reprod Update* **14**, 359-66.
- [718] Heilmann, L., Schorsch, M., Hahn, T. & Fareed, J. (2011). Antiphospholipid syndrome and pre-eclampsia. *Semin Thromb Hemost* **37**, 141-5.

- [719] Chen, Q., Guo, F., Hensby-Bennett, S., Stone, P. & Chamley, L. (2012). Antiphospholipid antibodies prolong the activation of endothelial cells induced by necrotic trophoblastic debris: implications for the pathogenesis of preeclampsia. *Placenta* **33**, 810-5.
- [720] Lefkou, E., Mamopoulos, A., Fragakis, N., Dagklis, T., Vosnakis, C., Nounopoulos, E., Rouso, D. & Girardi, G. (2014). Clinical improvement and successful pregnancy in a preeclamptic patient with antiphospholipid syndrome treated with pravastatin. *Hypertension* **63**, e118-9.
- [721] van Hoorn, M. E., Hague, W. M., van Pampus, M. G., Bezemer, D., de Vries, J. I. P. & investigators, F. (2016). Low-molecular-weight heparin and aspirin in the prevention of recurrent early-onset pre-eclampsia in women with antiphospholipid antibodies: the FRUIT-RCT. *Eur J Obstet Gynecol Reprod Biol* **197**, 168-73.
- [722] Amin, N. M. (2008). Antiphospholipid syndromes in infectious diseases. *Hematol Oncol Clin North Am* **22**, 131-43, vii-viii.
- [723] Asherson, R. A. & Cervera, R. (2003). Antiphospholipid antibodies and infections. *Ann Rheum Dis* **62**, 388-93.
- [724] García-Carrasco, M., Galarza-Maldonado, C., Mendoza-Pinto, C., Escarcega, R. O. & Cervera, R. (2009). Infections and the antiphospholipid syndrome. *Clin Rev Allergy Immunol* **36**, 104-8.
- [725] Sène, D., Piette, J. C. & Cacoub, P. (2008). Antiphospholipid antibodies, antiphospholipid syndrome and infections. *Autoimmun Rev* **7**, 272-7.
- [726] Shoenfeld, Y., Blank, M., Cervera, R., Font, J., Raschi, E. & Meroni, P. L. (2006). Infectious origin of the antiphospholipid syndrome. *Ann Rheum Dis* **65**, 2-6.
- [727] Zinger, H., Sherer, Y., Goddard, G., Berkun, Y., Barzilai, O., Agmon-Levin, N., Ram, M., Blank, M., Tincani, A., Rozman, B., Cervera, R. & Shoenfeld, Y. (2009). Common infectious agents prevalence in antiphospholipid syndrome. *Lupus* **18**, 1149-53.
- [728] Martínez-Zamora, M. A., Tassies, D., Carmona, F., Espinosa, G., Cervera, R., Reverter, J. C. & Balasch, J. (2010). Clot lysis time and thrombin activatable fibrinolysis inhibitor in severe preeclampsia with or without associated antiphospholipid antibodies. *J Reprod Immunol* **86**, 133-40.
- [729] Krone, K. A., Allen, K. L. & McCrae, K. R. (2010). Impaired fibrinolysis in the antiphospholipid syndrome. *Curr Rheumatol Rep* **12**, 53-7.
- [730] Lockshin, M. D. (2013). Anticoagulation in management of antiphospholipid antibody syndrome in pregnancy. *Clin Lab Med* **33**, 367-76.
- [731] Lockshin, M. D. (2013). Pregnancy and antiphospholipid syndrome. *Am J Reprod Immunol* **69**, 585-7.
- [732] Meroni, P. L., Chighizola, C. B., Rovelli, F. & Gerosa, M. (2014). Antiphospholipid syndrome in 2014: more clinical manifestations, novel pathogenic players and emerging biomarkers. *Arthritis Res Ther* **16**, 209.
- [733] Buhimschi, I. A., Nayeri, U. A., Zhao, G., Shook, L. L., Pensalfini, A., Funai, E. F., Bernstein, I. M., Glabe, C. G. & Buhimschi, C. S. (2014). Protein misfolding, congophilia, oligomerization, and defective amyloid processing in preeclampsia. *Sci Transl Med* **6**, 245ra92.
- [734] Jonas, S. M., Deserno, T. M., Buhimschi, C. S., Makin, J., Choma, M. A. & Buhimschi, I. A. (2016). Smartphone-based diagnostic for preeclampsia: an mHealth solution for administering the Congo Red Dot (CRD) test in settings with limited resources. *J Am Med Inform Assoc* **23**, 166-73.
- [735] Kouza, M., Banerji, A., Kolinski, A., Buhimschi, I. A. & Kloczkowski, A. (2017). Oligomerization of FVFLM peptides and their ability to inhibit beta amyloid peptides aggregation: consideration as a possible model. *Phys Chem Chem Phys* **19**, 2990-2999.
- [736] Clark, E. A. S., Silver, R. M. & Branch, D. W. (2007). Do antiphospholipid antibodies cause preeclampsia and HELLP syndrome? *Curr Rheumatol Rep* **9**, 219-25.
- [737] Saccone, G., Berghella, V., Maruotti, G. M., Ghi, T., Rizzo, G., Simonazzi, G., Rizzo, N., Facchinetti, F., Dall'Asta, A., Visentin, S., Sarno, L., Xodo, S., Bernabini, D., Monari, F., Roman, A., Eke, A. C., Hoxha, A., Ruffatti, A., Schuit, E., Martinelli, P. & group, P. w. (2017). Antiphospholipid antibody profile based obstetric outcomes of primary antiphospholipid syndrome: the PREGNANTS study. *Am J Obstet Gynecol* **216**, 525 e1-525 e12.

- [738] Horvath, S. E. & Daum, G. (2013). Lipids of mitochondria. *Prog Lipid Res* **52**, 590-614.
- [739] Mejia, E. M., Nguyen, H. & Hatch, G. M. (2014). Mammalian cardiolipin biosynthesis. *Chem Phys Lipids* **179**, 11-6.
- [740] Ren, M., Phoon, C. K. L. & Schlame, M. (2014). Metabolism and function of mitochondrial cardiolipin. *Prog Lipid Res* **55**, 1-16.
- [741] Hatch, G. M. (1998). Cardiolipin: biosynthesis, remodeling and trafficking in the heart and mammalian cells (Review). *Int J Mol Med* **1**, 33-41.
- [742] Saini-Chohan, H. K., Holmes, M. G., Chicco, A. J., Taylor, W. A., Moore, R. L., McCune, S. A., Hickson-Bick, D. L., Hatch, G. M. & Sparagna, G. C. (2009). Cardiolipin biosynthesis and remodeling enzymes are altered during development of heart failure. *J Lipid Res* **50**, 1600-8.
- [743] Chaban, Y., Boekema, E. J. & Dudkina, N. V. (2014). Structures of mitochondrial oxidative phosphorylation supercomplexes and mechanisms for their stabilisation. *Biochim Biophys Acta* **1837**, 418-26.
- [744] Mileykovskaya, E. & Dowhan, W. (2014). Cardiolipin-dependent formation of mitochondrial respiratory supercomplexes. *Chem Phys Lipids* **179**, 42-8.
- [745] Paradies, G., Paradies, V., De Benedictis, V., Ruggiero, F. M. & Petrosillo, G. (2014). Functional role of cardiolipin in mitochondrial bioenergetics. *Biochim Biophys Acta* **1837**, 408-17.
- [746] Paradies, G., Paradies, V., Ruggiero, F. M. & Petrosillo, G. (2014). Cardiolipin and mitochondrial function in health and disease. *Antioxid Redox Signal* **20**, 1925-53.
- [747] Dolinsky, V. W., Cole, L. K., Sparagna, G. C. & Hatch, G. M. (2016). Cardiac mitochondrial energy metabolism in heart failure: Role of cardiolipin and sirtuins. *Biochim Biophys Acta* **1861**, 1544-54.
- [748] Blank, M., Krause, I., Fridkin, M., Keller, N., Kopolovic, J., Goldberg, I., Tobar, A. & Shoenfeld, Y. (2002). Bacterial induction of autoantibodies to beta2-glycoprotein-I accounts for the infectious etiology of antiphospholipid syndrome. *J Clin Invest* **109**, 797-804.
- [749] Harel, M., Aron-Maor, A., Sherer, Y., Blank, M. & Shoenfeld, Y. (2005). The infectious etiology of the antiphospholipid syndrome: links between infection and autoimmunity. *Immunobiology* **210**, 743-7.
- [750] Cruz-Tapias, P., Blank, M., Anaya, J. M. & Shoenfeld, Y. (2012). Infections and vaccines in the etiology of antiphospholipid syndrome. *Curr Opin Rheumatol* **24**, 389-93.
- [751] Ebringer, A. & Rashid, T. (2009). Rheumatoid arthritis is caused by *Proteus*: the molecular mimicry theory and Karl Popper. *Front Biosci (Elite Ed)* **1**, 577-86.
- [752] Margulis, L. (1970). *Origin of eukaryotic cells*. Yale University Press, New Haven.
- [753] Bullerwell, C. E. & Gray, M. W. (2004). Evolution of the mitochondrial genome: protist connections to animals, fungi and plants. *Curr Opin Microbiol* **7**, 528-34.
- [754] Williams, K. P., Sobral, B. W. & Dickerman, A. W. (2007). A robust species tree for the alphaproteobacteria. *J Bacteriol* **189**, 4578-86.
- [755] Gray, M. W. (2012). Mitochondrial evolution. *Cold Spring Harb Perspect Biol* **4**, a011403.
- [756] Burger, G., Gray, M. W., Forget, L. & Lang, B. F. (2013). Strikingly bacteria-like and gene-rich mitochondrial genomes throughout jakobid protists. *Genome Biol Evol* **5**, 418-38.
- [757] Wang, Z. & Wu, M. (2015). An integrated phylogenomic approach toward pinpointing the origin of mitochondria. *Sci Rep* **5**, 7949.
- [758] Ball, S. G., Bhattacharya, D. & Weber, A. P. M. (2016). Pathogen to powerhouse. *Science* **351**, 659-60.
- [759] John, P. & Whatley, F. R. (1975). *Paracoccus denitrificans* and the evolutionary origin of the mitochondrion. *Nature* **254**, 495-8.
- [760] Matsumoto, K., Kusaka, J., Nishibori, A. & Hara, H. (2006). Lipid domains in bacterial membranes. *Mol Microbiol* **61**, 1110-7.
- [761] Epand, R. M. & Epand, R. F. (2009). Domains in bacterial membranes and the action of antimicrobial agents. *Mol Biosyst* **5**, 580-7.
- [762] Mileykovskaya, E. & Dowhan, W. (2009). Cardiolipin membrane domains in prokaryotes and eukaryotes. *Biochim Biophys Acta* **1788**, 2084-91.
- [763] Romantsov, T., Guan, Z. & Wood, J. M. (2009). Cardiolipin and the osmotic stress responses of bacteria. *Biochim Biophys Acta* **1788**, 2092-100.

- [764] Barák, I. & Muchová, K. (2013). The role of lipid domains in bacterial cell processes. *Int J Mol Sci* **14**, 4050-65.
- [765] Mukamolova, G. V., Yanopolskaya, N. D., Votyakova, T. V., Popov, V. I., Kaprelyants, A. S. & Kell, D. B. (1995). Biochemical changes accompanying the long-term starvation of *Micrococcus luteus* cells in spent growth medium. *Arch. Microbiol.* **163**, 373-379.
- [766] Kell, D. B. & Pretorius, E. (2014). Serum ferritin is an important disease marker, and is mainly a leakage product from damaged cells. *Metallomics* **6**, 748-773.
- [767] Agmon-Levin, N., Rosário, C., Katz, B. S., Zandman-Goddard, G., Meroni, P., Cervera, R., Stojanovich, L., Blank, M., Pierangeli, S., Praprotnik, S., Meis, E., Seguro, L. P., Ruffatti, A., Pengo, V., Tincani, A., Doria, A. & Shoenfeld, Y. (2013). Ferritin in the antiphospholipid syndrome and its catastrophic variant (cAPS). *Lupus* **22**, 1327-35.
- [768] Rosário, C., Zandman-Goddard, G., Meyron-Holtz, E. G., D'Cruz, D. P. & Shoenfeld, Y. (2013). The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. *BMC Med* **11**, 185.
- [769] Andrade, S. E., Gurwitz, J. H., Davis, R. L., Chan, K. A., Finkelstein, J. A., Fortman, K., McPhillips, H., Raebel, M. A., Roblin, D., Smith, D. H., Yood, M. U., Morse, A. N. & Platt, R. (2004). Prescription drug use in pregnancy. *Am J Obstet Gynecol* **191**, 398-407.
- [770] Egen-Lappe, V. & Hasford, J. (2004). Drug prescription in pregnancy: analysis of a large statutory sickness fund population. *Eur J Clin Pharmacol* **60**, 659-66.
- [771] Riley, E. H., Fuentes-Afflick, E., Jackson, R. A., Escobar, G. J., Brawarsky, P., Schreiber, M. & Haas, J. S. (2005). Correlates of prescription drug use during pregnancy. *J Womens Health (Larchmt)* **14**, 401-9.
- [772] Daw, J. R., Hanley, G. E., Greyson, D. L. & Morgan, S. G. (2011). Prescription drug use during pregnancy in developed countries: a systematic review. *Pharmacoepidemiol Drug Saf* **20**, 895-902.
- [773] Mitchell, A. A., Gilboa, S. M., Werler, M. M., Kelley, K. E., Louik, C., Hernández-Díaz, S. & National Birth Defects Prevention Study. (2011). Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. *Am J Obstet Gynecol* **205**, 51 e1-8.
- [774] Daw, J. R., Mintzes, B., Law, M. R., Hanley, G. E. & Morgan, S. G. (2012). Prescription drug use in pregnancy: a retrospective, population-based study in British Columbia, Canada (2001-2006). *Clin Ther* **34**, 239-249 e2.
- [775] Cea-Soriano, L., Garcia Rodríguez, L. A., Fernández Cantero, O. & Hernández-Díaz, S. (2013). Challenges of using primary care electronic medical records in the UK to study medications in pregnancy. *Pharmacoepidemiol Drug Saf* **22**, 977-85.
- [776] Valent, F., Gongolo, F., Deroma, L. & Zanier, L. (2015). Prescription of systemic antibiotics during pregnancy in primary care in Friuli Venezia Giulia, Northeastern Italy. *J Matern Fetal Neonatal Med* **28**, 210-5.
- [777] Palmsten, K., Hernández-Díaz, S., Chambers, C. D., Mogun, H., Lai, S., Gilmer, T. P. & Huybrechts, K. F. (2015). The most commonly dispensed prescription medications among pregnant women enrolled in the U.S. Medicaid program. *Obstet Gynecol* **126**, 465-73.
- [778] Smolina, K., Hanley, G. E., Mintzes, B., Oberlander, T. F. & Morgan, S. (2015). Trends and Determinants of Prescription Drug Use during Pregnancy and Postpartum in British Columbia, 2002-2011: A Population-Based Cohort Study. *PLoS One* **10**, e0128312.
- [779] Heikkilä, A. M. (1993). Antibiotics in pregnancy--a prospective cohort study on the policy of antibiotic prescription. *Ann Med* **25**, 467-71.
- [780] Santos, F., Oraichi, D. & Bérard, A. (2010). Prevalence and predictors of anti-infective use during pregnancy. *Pharmacoepidemiol Drug Saf* **19**, 418-27.
- [781] de Jonge, L., Bos, H. J., van Langen, I. M., de Jong-van den Berg, L. T. W. & Bakker, M. K. (2014). Antibiotics prescribed before, during and after pregnancy in the Netherlands: a drug utilization study. *Pharmacoepidemiol Drug Saf* **23**, 60-8.
- [782] Bookstaver, P. B., Bland, C. M., Griffin, B., Stover, K. R., Eiland, L. S. & McLaughlin, M. (2015). A Review of Antibiotic Use in Pregnancy. *Pharmacotherapy* **35**, 1052-62.
- [783] Calogero, A. E., Condorelli, R. A., Russo, G. I. & Vignera, S. (2017). Conservative Nonhormonal Options for the Treatment of Male Infertility: Antibiotics, Anti-Inflammatory Drugs, and Antioxidants. *Biomed Res Int* **2017**, 4650182.
- [784] Kabir, S. (2007). The current status of *Helicobacter pylori* vaccines: a review. *Helicobacter* **12**, 89-102.

- [785] D'Elia, M. M. & Czinn, S. J. (2014). Immunity, inflammation, and vaccines for *Helicobacter pylori*. *Helicobacter* **19 Suppl 1**, 19-26.
- [786] Ng, G. Z., Chionh, Y. T. & Sutton, P. (2014). Vaccine-mediated protection against *Helicobacter pylori* is not associated with increased salivary cytokine or mucin expression. *Helicobacter* **19**, 48-54.
- [787] Sutton, P. & Chionh, Y. T. (2013). Why can't we make an effective vaccine against *Helicobacter pylori*? *Expert Rev Vaccines* **12**, 433-41.
- [788] Grixti, J., O'Hagan, S., Day, P. J. & Kell, D. B. (2017). Enhancing drug efficacy and therapeutic index through cheminformatics-based selection of small molecule binary weapons that improve transporter-mediated targeting: a cytotoxicity system based on gemcitabine. *Front Pharmacol* **8**, 155.
- [789] Borisy, A. A., Elliott, P. J., Hurst, N. W., Lee, M. S., Lehar, J., Price, E. R., Serbedzija, G., Zimmermann, G. R., Foley, M. A., Stockwell, B. R. & Keith, C. T. (2003). Systematic discovery of multicomponent therapeutics. *Proc Natl Acad Sci U S A* **100**, 7977-82.
- [790] Lehar, J., Krueger, A. S., Avery, W., Heilbut, A. M., Johansen, L. M., Price, E. R., Rickles, R. J., Short, G. F., 3rd, Staunton, J. E., Jin, X., Lee, M. S., Zimmermann, G. R. & Borisy, A. A. (2009). Synergistic drug combinations tend to improve therapeutically relevant selectivity. *Nat Biotechnol* **27**, 659-66.
- [791] Kell, D. B. (2009). Iron behaving badly: inappropriate iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases. *BMC Med Genom* **2**, 2.
- [792] Kell, D. B. (2010). Towards a unifying, systems biology understanding of large-scale cellular death and destruction caused by poorly liganded iron: Parkinson's, Huntington's, Alzheimer's, prions, bactericides, chemical toxicology and others as examples. *Arch Toxicol* **577**, 825-889.
- [793] Carey, N. (2012). *The epigenetics revolution*. Icon Books, London.
- [794] Day, J., Savani, S., Krempel, B. D., Nguyen, M. & Kitlinska, J. B. (2016). Influence of paternal preconception exposures on their offspring: through epigenetics to phenotype. *Am J Stem Cells* **5**, 11-8.
- [795] Abbasi, J. (2017). The Paternal Epigenome Makes Its Mark. *JAMA*.
- [796] Bonney, E. A. (2013). Demystifying animal models of adverse pregnancy outcomes: touching bench and bedside. *Am J Reprod Immunol* **69**, 567-84.
- [797] LaMarca, B., Amaral, L. M., Harmon, A. C., Cornelius, D. C., Faulkner, J. L. & Cunningham, M. W., Jr. (2016). Placental Ischemia and Resultant Phenotype in Animal Models of Preeclampsia. *Curr Hypertens Rep* **18**, 38.
- [798] Kenny, L. C., Broadhurst, D. I., Dunn, W., Brown, M., Francis-McIntyre, S., North, R. A., McGowan, L., Roberts, C., Cooper, G. J. S., Kell, D. B. & Philip N Baker on behalf of the SCOPE consortium. (2010). Robust early pregnancy prediction of later preeclampsia using metabolomic biomarkers *Hypertension* **56**, 741-749.
- [799] Kell, D. B. & Oliver, S. G. (2016). The metabolome 18 years on: a concept comes of age. *Metabolomics* **12**, 148.
- [800] Infectious Diseases Society of America, Spellberg, B., Blaser, M., Guidos, R. J., Boucher, H. W., Bradley, J. S., Eisenstein, B. I., Gerding, D., Lynfield, R., Reller, L. B., Rex, J., Schwartz, D., Septimus, E., Tenover, F. C. & Gilbert, D. N. (2011). Combating antimicrobial resistance: policy recommendations to save lives. *Clin Infect Dis* **52 Suppl 5**, S397-428.
- [801] Gelband, H. & Laxminarayan, R. (2015). Tackling antimicrobial resistance at global and local scales. *Trends Microbiol* **23**, 524-6.
- [802] Laxminarayan, R., Sridhar, D., Blaser, M., Wang, M. & Woolhouse, M. (2016). Achieving global targets for antimicrobial resistance. *Science* **353**, 874-5.
- [803] Coates, A. R. M. & Hu, Y. (2006). New strategies for antibacterial drug design: targeting non-multiplying latent bacteria. *Drugs R D* **7**, 133-51.
- [804] Coates, A. R., Halls, G. & Hu, Y. (2011). Novel classes of antibiotics or more of the same? *Br J Pharmacol* **163**, 184-94.
- [805] Hu, Y., Liu, A., Ortega-Muro, F., Alameda-Martin, L., Mitchison, D. & Coates, A. (2015). High-dose rifampicin kills persisters, shortens treatment duration, and reduces relapse rate *in vitro* and *in vivo*. *Front Microbiol* **6**, 641.