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Reply: In vitro culture conditions, antiphospholipid antibodies and trophoblast function

Sir,

We thank Drs Clark and Laskin for their interest in our recently published systematic review of the effects of antiphospholipid antibodies on cultured placental cells in vitro. We agree with many of the authors’ comments and their suggestions for future investigations. However, in suggesting that trophoblast plugs prevent antiphospholipid antibodies accessing the placenta in early gestation, we believe that Drs Clark and Laskin have misinterpreted the reports of trophoblast plugs in the uterine spiral arteries.

Firstly, it has been shown that potentially as few as 20% of spiral arteries are fully plugged during the first trimester of human pregnancy (Meekins et al., 1997), which if true, means maternal blood-borne antibodies would readily access early gestation placentae. Secondly, trophoblast plugs in the spiral arteries are widely agreed to be only loosely cohesive (Boyd and Hamilton, 1970; Ramsey and Donner, 1980). This loose cohesion means that while the plugs prevent the passage of maternal red blood cells into the intervillous space, maternal plasma may still pass through the plugs to access the placenta. Supporting this, hysteroscopic examination reveals that placental villi are bathed in a clear fluid prior to 12 weeks of gestation (Jaffe et al., 1997) and histologic specimens of implantation sites from as early as 50 days gestation show clear tracks of fluid leading from the spiral arteries to the intervillous space (Burton et al., 1999). The flow of maternal plasma to and from the placenta is corroborated by the finding of substantial numbers of placenta-derived extracellular vesicles (syncytial nuclear aggregates, micro- and nanovesicles) in the maternal peripheral blood from as early as 6 weeks of gestation (Covone et al., 1984; Knight et al., 1998; Askelund and Chamley, 2011; Salomon et al., 2014). Thus, unlike maternal red blood cells, soluble factors including antiphospholipid antibodies have access to the first trimester placenta despite the presence of trophoblast plugs in the spiral arteries. Therefore, these autoantibodies may have direct deleterious effects on the placenta from the beginning of placental development.

References


B cell responses in pregnancy and vaccine efficacy

Sir,

We read with great interest the review by Faucette et al. (2015) regarding the safety and impact of maternal immunization during pregnancy. This review is an exhaustive work encompassing the epidemiological, physiological and practical aspects of this critical global health issue. They argue that significant alteration of the humoral response occurs during pregnancy that could hamper vaccine efficacy. They propose that estrogens and pregnancy hormones have significant impact on B cells development and function. However, most of the evidence comes from murine studies or in vitro models. In humans, quantitative changes in the B cell compartment during pregnancy have indeed been described, although these alterations seem rather limited. The viral immunity and pregnancy (VIP) study that prospectively assessed the immune parameters of 50 women during pregnancy and in the post-partum period only showed a moderate but significant decrease in the absolute B cells numbers during the third trimester (Kraus et al., 2012). However, these quantitative changes do not seem to alter B cell responses during pregnancy. Indeed, both immunological and vaccine studies indicate that efficient memory and plasma cells responses can be induced during pregnancy. We have studied the proportion of B cell subsets in pregnant women with and without cytomegalovirus (CMV) infection. While pregnant women with primary CMV infection had prolonged expansion of activated and atypical memory B cells, no change in the proportion of peripheral blood B cells subsets was observed between healthy pregnant women during the first trimester, second trimester and immediate post-partum period and non-pregnant women (Dauby et al., 2014). The VIP
study also assessed the response to inactivated influenza vaccine and found similar seroconversion rates during the three trimesters of pregnancy (Sperling et al., 2012). Finally, the ability of pregnant women to respond to recall antigens was recently demonstrated in a randomized controlled trial of tetanus–diphtheria–acellular pertussis immunization. The immunogenicity was shown to be similar in pregnant and non-pregnant women (Munoz et al., 2014). In summary, B cell compartments, including naïve and memory B cells, appear poorly affected by pregnancy; response to both neo and recall antigens can be elicited during pregnancy making maternal immunization an important strategy to improve global maternal, newborn and child health.

Conflict of interest

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References


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Reply: Maternal vaccination: moving the science forward

Sir,
We thank Dr Dauby for his interest in our review (Faucette et al., 2015), and share his appreciation of the progress and confidence in the promise of maternal vaccination as a strategy to combat maternal and neonatal infections. Despite the success of selected maternal vaccines, we contend that pregnancy-associated immune modulations could cause suboptimal or qualitatively different vaccine responses. Supporting this notion are the numerous studies showing that both human (Christiansen et al., 1976; Moore et al., 1983; Valdimarsson et al., 1983; Iwani et al., 1988; Watanabe et al., 1997; Mahmoud et al., 2001; Kraus et al., 2012; Sperling et al., 2012) and mouse pregnancies (Medina and Kincade, 1994) are associated with substantial modulations in the B cell compartment. Dr Dauby claimed that such changes in B cells during human pregnancy seemed rather limited and did not appear to affect B cell function, as suggested by recent studies showing similar proportions of first and second trimester B cell subsets (Dauby et al., 2014), rate of seroconversion (Sperling et al., 2012) and immunogenicity (Munoz et al., 2014) in response to vaccination in pregnant and non-pregnant women. It is, however, important to note that the proportion values do not provide direct information on the absolute numbers of B cell subsets. Furthermore, seroconversion rate or immunogenicity does not reflect the diversity or quality of the humoral immune repertoire, such as the degree of somatic hypermutation or neutralizing function. Therefore, the impact of pregnancy-associated changes in the B cell compartment on humoral immune function remains to be carefully elucidated.

Dr Dauby further suggested that B cell-associated quantitative changes occur only in the third trimester, based on findings from his lab and others (Kraus et al., 2012; Dauby et al., 2014). The reduced numbers of circulating B cells have been well documented in the third trimester, but a number of studies found that the reduction in circulating B cell numbers occurred earlier in pregnancy (Moore et al., 1983; Valdimarsson et al., 1983; Iwani et al., 1988; Watanabe et al., 1997). Considering that the optimal timing of Tetanus, diphtheria and pertussis vaccination (Tdap) recommended by the Centers for Disease Control and Prevention is between 27 and 36 weeks of gestation (Centers for Disease Control and Prevention, 2013) and that the highest trivalent IIV vaccine response rate was seen in the third trimester (Sperling et al., 2012), the substantial reduction in circulating B cell numbers consistently found in the third trimester is likely to impact vaccine response during this critical window. While many studies on the role of reproductive hormones, such as estrogen, that are implicated in modulating B cell function during pregnancy was conducted in mice, the effect of estrogen on human B cell maturation, albeit indirectly, parallels the findings in mouse B cells (Paavonen et al., 1981). In conclusion, due to the complexity of humoral immune modulation, a paucity of data on the B cell compartment in systemic and mucosal secondary lymphoid organs, which are the inductive sites of vaccine immunity distinct from the circulation, and a lack of molecular and functional assessment of the vaccine-induced antibody repertoire during pregnancy, it is presumptuous to conclude that ‘B cell compartments, including naïve and memory B cells, appear poorly affected by pregnancy and response to both neo and recall antigens is intact during pregnancy’. Coupled with the heightened ethical and medical concerns of vaccine safety in pregnancy, it is important to exercise caution and combine clinical readouts with basic immunological insights in the development, evaluation and improvement of maternal vaccines, particularly for less well-studied vaccines and in women susceptible to high-risk pregnancies, such that this promising public health strategy can be made safer and more efficient to broader populations against a wider range of infections.

Conflict of interest

The authors declare no competing financial interests.

References

Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap)