Spiral arteries. Therefore, these autoantibodies may have direct deleterious effects on first trimester placenta despite the presence of trophoblast plugs in the spiral arteries. This implies that potentially as few as 20% of spiral arteries are fully plugged during the first trimester of human pregnancy. 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 placenta. 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, histoscopic 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 (Daubey et al., 2014). The VIP

**Letters to the Editor**

Re: *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 placenta. 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, histoscopic 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.