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IFPA meeting 2015 workshop report IV: Placenta and obesity; stem cells of the feto-maternal interface; placental immunobiology and infection

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ABSTRACT

Workshops are an important part of the IFPA annual meeting as they allow for discussion of specialised topics. At the 2015 IFPA annual meeting there were 12 themed workshops, three of which are summarized in this report. These workshops related to various aspects of placental biology and collectively covered areas of obesity and the placenta, stem cells of the feto-maternal interface, and placental immunobiology and infection.

1. Placenta and obesity

Chairs: Terry Morgan and Yee Khong.
Presenters: Yee Khong, Terry Morgan, Sarah Cash and Kevin Kolahi.

1.1. Outline

The objectives of this workshop were to discuss the current

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obesity epidemic, which has led to an increase in the prevalence of gestational diabetes and may be a significant independent risk factor for preterm birth and stillbirth. The impact on developmental programming is only in the early stages of investigation and placental pathology may provide important insights into key disease mechanisms.

1.2. Summary

Yee Khong discussed the relationship between obesity and stillbirth. Obesity, defined as having a body mass index (BMI) of >30.0 kg/m^2, is a worldwide health epidemic, with over 30% of women of reproductive age obese, and almost 1 in 1000 pregnant women considered super obese (BMI $\geq$ 50) [1]. Maternal obesity is associated with numerous maternal, neonatal and labour complications. There is a positive dose response relationship between increasing maternal BMI and relative risk of fetal birth, stillbirth, and neonatal, perinatal, and infant death, i.e. the relative risk increases with each incremental increase of BMI unit [2]. Biological mechanisms include a role for the placenta through inflammatory, vascular and endothelial dysfunction, and hyperlipidaemia.

Terry Morgan presented work from his group studying the effects of obesity on uteroplacental blood flow and placental pathology in women and non-human primates. Contrast-enhanced imaging techniques combined with flow cytometry and molecular analysis allow them to correlate blood flow with immunologic regulators of uterine spiral artery remodeling in the placental bed. Their data suggest obesity leads to placental insufficiency, which is evident in abnormal uteroplacental blood flow and placental pathology. Uterine natural killer cell activation appears to be decreased in obese women and there may be a relationship with abnormal T-cell polarization in the late first trimester. Dr. Morgan pointed out that we are only beginning to understand why and how obesity affects reproductive immunology.

In her presentation, Sarah Cash noted that women with high BMI are at risk of adverse pregnancy outcomes and their placentas demonstrate an increased rate of histopathological lesions compared to lean controls. The effect of an antenatal dietary and lifestyle intervention for women with high BMI was assessed. 188 placentas were collected and examined for morphometry and histopathology, and inflammation was quantified with an inflammatory score. There was no significant effect of gestational weight gain on placental pathology or inflammation. It was concluded that pre-gestational BMI seems to be the most important indicator of weight-related pregnancy pathology.

Kevin Kolahi talked about a study in which the hypothesis that syncytiotrophoblast is the primary site of fatty acid uptake, esterification and lipid droplet synthesis was tested. Fluorescent fatty acid analogues and confocal microscopy were used to quantify fatty acid uptake in real-time in isolated term human placental explants and in cultured cytotrophoblast. Surprisingly, the cytotrophoblast layer was the principle site of long-chain fatty acid esterification and exclusively synthesized lipid droplets. Cytotrophoblasts were not previously known to have physiological importance in fat uptake and metabolism. This study provides new evidence that the cytotrophoblast layer and not the syncytiotrophoblast is the primary site of fatty acid esterification.

1.3. Conclusions

This workshop provided new insights into how maternal obesity may affect uterine vascular remodeling, blood flow to the placenta, placental metabolism, and placental histopathology related to pregnancy complications in obese women. We are only in the early stages of studying the underlying mechanisms, but the significance related to preterm birth and stillbirth is clear.

2. Stem cells of the feto-maternal interface

Chairs: Bill Kalionis, Larry Chamley, Mohamed H. Abumaree.

Speakers: Rebecca A. Pelekanos, Teena Gamage, Rebecca Lim, Abdulaziz Almutairi, Mohamed H. Abumaree, Joanna James, Abbas Shafiee.

2.1. Outline

The placenta and uterus are sources of many stem cell populations including cytotrophoblast, mesenchymal, endothelial, haematopoietic and epithelial stem cells. Some of these stem cell populations are intensively studied for their potential use in reparative and regenerative medicine. Accumulating evidence suggests that stem cells are an important new player in normal and pathological development of the placenta and uterus. This workshop showcased both basic and applied research on placental and uterine stem cells.

2.2. Summary

Rebecca Pelekanos discussed the controversies surrounding the isolation of pure populations of fetal or maternal mesenchymal stem/stromal cells (MSC) from the human placental chorion. A review of published procedures did not clearly establish a methodology to isolate pure fetal MSC from the chorion. Data were presented explaining how to decrease maternal cell contamination and enhance fetal MSC proliferation by explant culture. Finally, advice was given to researchers to thoroughly describe their MSC isolation procedures, and to characterize the origin and properties of MSC populations. This will facilitate reproducibility of findings and enhance the clinical translation of placental MSCs.

Teena Gamage presented unpublished data on side-population trophoblast; a candidate human trophoblast stem cell population. Side-population trophoblast exhibit stem-like characteristics including expression of pluripotency and murine stem cell markers and were first isolated from human first trimester villi by James et al. [3]. More recently, enriched populations of side-population trophoblast were isolated from term placental villi. At present, side-population trophoblast can only be maintained in the short-term, although their survival is enhanced by culture on a laminin matrix in low oxygen, serum-free conditions. Further optimisation is required to establish long-term culture, which will allow their stem-like functions to be assessed.

Rebecca Lim reported on human amnion epithelial cells (hAECs), which are profoundly immunomodulatory, and this is key to their reparative properties. She focused on recent efforts to unpick the interactions between hAECs and immune cell subsets during the resolution of injury. It was shown that hAEC-derived TGF-β is a key trigger of Treg differentiation and that macrophage polarization during hAEC-mediated lung repair is dependent on this event. Furthermore, administration of hAECs results in an *in vivo* expansion of Tregs.

Abdulaziz Almutairi reported on mesenchymal stem cells derived from the chorionic villi of human term placenta (pMSCs), which have drawn significant interest because of their potential to differentiate into different cell types and their immunomodulatory functions. These properties are essential for their use in regenerative medicine. It was shown that pMSCs can inhibit IL-2-induced proliferation of NK cells and only IL-2-stimulated NK cells can lyse pMSCs. In addition, it was demonstrated that the activating NK receptors NKp30, NKG2D, and NKp44 are the major receptors mediating NK-mediated lysis of pMSCs and pMSCs do not affect the

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