Accepted Manuscript

Placental metabolism and disease

Luis Sobrevia

PII: S0143-4004(18)31037-3

DOI: 10.1016/j.placenta.2018.09.001

Reference: YPLAC 3873

To appear in: *Placenta*

Please cite this article as: Sobrevia L, Placental metabolism and disease, *Placenta* (2018), doi: 10.1016/j.placenta.2018.09.001.

Editorial

Placental metabolism and disease

Introduction

The placenta is recognised as an organ that plays a vital role as a metabolic and a physical barrier in the foetoplacental unit. Several metabolic substrates and other molecules cross the placenta from the mother to the foetus and vice versa. This physiological phenomenon is considered as a mechanism of communication between the mother and the foetus. The exchange of metabolic signals between the mother and the foetus is mutually beneficial and secures the development and growth of the foetus as well as the wellbeing of the mother during and after pregnancy. The primary cell types in the placenta are trophoblasts (which form the syncytiotrophoblasts) as well as the vascular endothelium and smooth muscle (forming the placental macrovascular and microvascular net). The architecture of these cells in the placenta imposes structural and metabolic barriers for the transfer of metabolic substrates (e.g. oxygen, D-glucose, amino acids and vitamins), hormones (e.g. thyroid hormones), toxins (e.g. carbon dioxide) and waste material. It is also an organ that transfers immunity and releases hormones (e.g. oestrogen, progesterone, placental lactogen and placental variant growth hormone (GH-V)) [1] and extracellular vesicles including nanovesicles (i.e. exosomes) into the foetal [2] and maternal [3] circulation.

Pregnancy is a physiological phenomenon that could initiate in healthy women, thus leading to a healthy pregnancy and a healthy newborn and mother. However, women who

show pre-gestational diseases or metabolic disturbances develop a condition that results in an adverse outcome for the mother and the foetus. Further, pregnancy disorders such as preeclampsia and gestational diabetes mellitus (GDM) are associated with an adverse intrauterine environment for foetal development and growth. These pathological conditions result in altered foetoplacental vascular function and adverse newborn outcome, thereby making them prone to develop diseases in their childhood, adolescence and adulthood. It is worrying to know that the worldwide prevalence of type 1 (T1DM) and type 2 (T2DM) diabetes mellitus and obesity increased significantly in the last decade and at higher rates than before [4,5]. In developing countries like Chile in South America, the prevalence of diabetes mellitus increased to ~44% in the last 6-7 years in women during their reproductive age [6]. Additionally, the prevalence of overweight (body mass index (BMI) 25–29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) [5] in this group of women increased to ~9% and ~23%, respectively, during the same period [6]. Thus, a higher risk of an unhealthy pregnancy along with diabetes mellitus- and pre-gestational maternal obesity (PGMO)-associated adverse outcomes (maternal, foetal, newborn, child and adult) in Chilean women (and worldwide) is likely.

Patients who are obese and develop T2DM, with or without associated risk factors, are referred to as having ‘diabesity’ [7,8]. Patients with diabesity show an abnormal functioning of the cardiovascular system worsening its response to vasodilators (e.g. insulin and adenosine) compared with patients with obesity or T2DM only [8,9]. With regard to pre-GDM and obesity, GDM prevalence is also increasing worldwide. Thus, PGMO is a risk factor that could cause or associate with the GDM-related deleterious effects seen in the mother, foetus and newborn. However, it is unknown whether pregnant women with

PGMO, without T2DM or T1DM, who develop GDM (herein referred to as 'gestational diabesity') could differentially affect or worsen the vascular function in the human placenta caused by maternal obesity or GDM only.

Contributions to the issue

Common factors in preeclampsia, intrauterine growth restriction, GDM, PGMO and supraphysiological maternal gestational weight gain (spGWG) include altered transport of L-arginine and adenosine, modified nitric oxide (NO) synthesis and bioavailability, miss-handling of magnesium (Mg^{2+}) by the placental tissue and dyslipidaemia and an imbalanced redox state. In this special issue of Placenta, a series of review articles concerning various aspects associated with pregnancy and foetoplacental function in metabolic diseases is discussed. **Professor David Hill** (Canada) describes that placental lactogen and GH-V are factors involved in the foetal nutritional availability, thereby causing modifications in the insulin/insulin-like growth factor axis [10]. The latter is a concept that seems crucial in understanding the physiology and pathophysiology of the insulin signalling in the placental vasculature. Insulin resistance is seen in the mother and the foetus in GDM, and several essential signalling molecules associated with insulin receptor B involved in the downregulation of the insulin receptor substrates 1 and 2 – protein kinase B/Akt (Akt) branch have been reported [11,12]. Interestingly, increased GH-V is associated with peripheral insulin resistance, a phenomenon likely counter-balanced by an expansion of maternal pancreatic β-cell mass. This review proposes that maternal obesity during pregnancy is a factor that induces trans-differentiation of pancreatic α to β cells, which could result in increased β-cell mass in diabetes during pregnancy. The latter is

a mechanism proposed to prevent the onset of gestational diabetes; however, because the lack of information addressing the effect of PGMO as an inductor of GDM in humans, this mechanism is still waiting for a proper characterisation in gestational diabesity.

Presently, it is better known that maternal metabolic disorders during pregnancy correlated with modifications in the foetus and newborn, thereby resulting in the programming of adulthood health and disease. **Dr Bredford Kerr and colleagues** (Chile) proposed in their review that epigenetic modifications are capable of changing the expression of metabolism-related genes [13]. Modified expression of several genes in the human placenta associated with the transport and metabolism of nutrients, therefore affecting the foetal growth, is proposed to result from epigenetic mechanisms. Epigenetic changes include altered methylation of CpG dinucleotides, post-translational modifications of histones, methylation in CpH dinucleotides (where H is adenine, thymine or cytosine) and micro RNA (miRNA) expression. Interestingly, diseases during pregnancy, such as maternal dyslipidaemia, PGMO or maternal obesity resulting from spGWG, and GDM course with an altered uptake of essential metabolic substrates including L-arginine and adenosine thus alter the generation of NO in the placental vasculature [14-17]. Figure 1 summarises the epigenetic modifications reported in the mother, placenta, newborn, childhood and adulthood in these metabolic alterations that occurred during pregnancy. Whether changes in the transport of metabolic substrates in the placenta are due to epigenetic modifications is not yet fully understood.

Interestingly, aberrant expression of placental genes involved in oxidative stress and inflammation, among others, has been explained by epigenetic modifications [18,19]. The review by **Professor Hillebrands and colleagues** (The Netherlands) summarised the findings available in the literature, thus addressing the role of oxidative stress in

pregnancies with preeclampsia [20]. The role or involvement of superoxide anion, hydrogen peroxide and peroxynitrite is reported in the pathological placenta for each trimester of pregnancy. Placental adaptation to hypoxia and mechanisms regarding oxidative stress are described in this review. Additionally, understanding the genesis and causes of the generation of oxidative stress markers in preeclampsia will reach to a stage where associated biomarkers could be used as a tool to predict potential significant disturbances in the redox state in the placenta, which alter foetal development. Gasotransmitters are known for their role in regulating vascular tone in the placenta. Because oxidative stress is a condition that could result in abolishing the biological actions of NO, carbon monoxide and hydrogen sulphide, it is proposed that the bioavailability of these molecules could be altered in diseases, thereby affecting the function of the placenta.

Hydrogen sulphide and NO not only regulate vascular tone but are also involved in immunological and angiogenic processes. These metabolic effects are in fact a topic touched in the review by **Dr Faas** and **Professor Paul De Vos** (The Netherlands), thus addressing the available literature about immune cells, specifically uterine natural killer (uNK) cells, and their role in the development of the placental bed [21]. These cells regulate the immune function in conjunction with macrophages, dendritic cells and mast cells in the placenta. Further, these cells modulate trophoblast invasion, angiogenesis and spiral artery remodelling, thus playing a pivotal role in preeclampsia where decreased trophoblast invasion and spiral artery remodelling are reported. Interestingly, this phenomenon is likely due to inhibition of matrix metalloproteinases resulting from the overexpression of the reversion-inducing cysteine-rich protein with Kazal motifs in the human placenta in preeclampsia [22].

Placental vasculogenesis is a physiological mechanism required in gestation, and it

could deviate from the normal at any time depending on the microenvironment in pregnancy. The review by **Dr Azevedo Portilho** and **Dr Pelajo-Machado** (Brazil) shows results in the mouse placenta where a putative haematopoietic foci in the placenta labyrinth were detected [23]. According to the available literature and a detailed analysis of their results, the authors propose that the mouse placenta produces haematopoietic stem/progenitor cells and primitive erythrocytes perhaps were involved or responsible for a rapid, mid-pregnancy, foetal growth trajectory. They also suggest that it may be a close origin of haematopoietic and endothelial cells in the mouse placenta. Furthermore, the findings described by this group indicate that placental erythropoietic foci arise in situ rather than from circulating cells. The possibility that precursors may generate into haematopoietic and endothelial cells ending in the formation of new vessels (i.e. angiogenesis) in the placenta is discussed. In another topic, **Dr Chiarello and colleagues** highlighted the fact that administering Mg^{2+} salts to women with preeclampsia is a routine procedure in clinical practice with an aim to reduce the pathophysiological consequences of preeclampsia and eclampsia [24]. In women with preeclampsia, Mg^{2+} sulphate and Mg^{2+} gluconate had been used, thereby resulting in the relaxation of the vascular smooth muscle perhaps because of an increase in NO synthesis due to stabilisation of the cofactor for endothelial NO synthase tetrahydrobiopterin and prevention of its oxidation. Several mechanisms are currently proposed for the beneficial effects of Mg^{2+} sulphate and are listed in Table 1 in the review. Interestingly, the expression of Mg^{2+} transporters such as Na^{+}/Mg^{2+} exchangers (coded by *SLC41A1*) is increased in preeclampsia and a transplacental transfer of this cation is seen. Indeed, the trophoblast may contain lower levels of Mg^{2+} owing to hyperactivity of these and other membrane transporters. In general, it is proposed that Mg^{2+} restores endothelial dysfunction seen in preeclampsia, thereby

inactivating brain N-methyl-D-aspartate receptors and reducing the inflammatory response and oxidative stress. The information discussed in this review is summarized in Figure 1.

Conclusions

As PGMO and diabetes mellitus are metabolic alterations whose worldwide prevalence is increasing in the last decade, studies regarding the consequences of these conditions in placental function and foetal development are required. This series of review articles is a sample of the mechanisms involved in placental development and the consequences of an adverse intrauterine environment for the developing foetus. These changes result in a programming phenomenon that is transduced into diseases in the newborn, childhood, adolescence and adulthood. Equally, the mother presents post-pregnancy diseases including diabetes mellitus and hypertension. The mechanisms associated with insulin resistance may include a restructuration of the functioning of the pancreas by inducing trans-differentiation of pancreatic α to β cells; these phenomena may cause or also be dependent on epigenetic modifications in the diseases of pregnancy. A factor always present in the metabolic adaptations in the placenta and the whole body is a proper oxidative stress balance between pro- and anti-oxidative mechanisms. The placenta has to adapt to these changes in pathologies such as preeclampsia and GDM. One of the mechanisms is angiogenesis, perhaps with the generation of new endothelial cells from placental haematopoietic cells, for supplying more efficiently the constant demand of nutrients or salts needed for proper development (such as Mg^{2+}) by the growing foetus. Therefore, the gestation period is commanded by the healthiness of the placenta, and both the mother and the foetus communicate to make this process a successful one.

Conflict of interest

There is no conflict of interest.

Acknowledgements

The papers included in this special issue were communicated at the joint meeting of the Latin-American Society for Placenta and Fetomaternal Research (SLIMP) – Sociedad Chilena de Ciencias Fisiológicas (April 2017, Puerto Varas, Chile). I thank all the authors who contributed to this special issue. Support was provided by the Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT 1150377), Sociedad Chilena de Ciencias Fisiológicas, Vicerrectorate of Research and School of Medicine of the Pontificia Universidad Católica de Chile, Comisión Nacional para la Investigación en Ciencia y Tecnología (CONICYT) (Chile) and Placenta Association of the Americas (PAA)-International Federation of Placenta Associations (IFPA).

Professor Luis Sobrevia, *FPhysiol*

Guest Editor *Placenta*

Cellular and Molecular Physiology Laboratory (CMPL)

Department of Obstetrics

Division of Obstetrics and Gynaecology

School of Medicine, Faculty of Medicine

Pontificia Universidad Católica de Chile

Santiago 8330024, Chile

e-Mail: lsobrevia@uc.cl

Honorary Professor

Department of Physiology

Faculty of Pharmacy

Universidad de Sevilla

Seville E-41012, Spain.

Honorary Professor

University of Queensland Centre for Clinical Research (UQCCR)

Faculty of Medicine and Biomedical Sciences

University of Queensland

Herston, QLD 4029, Queensland, Australia.

205

References

[1] S.K. Griffiths, J.P. Campbell, Placental structure, function and drug transfer, Continuing Education in Anaesthesia Critical Care & Pain 15 (2015) 84–89.

210 [2] T. Sáez, P. de Vos, L. Sobrevia, M.M. Faas, Is there a role for exosomes in foetoplacental endothelial dysfunction in gestational diabetes mellitus? Placenta 61 (2018) 48–54.

[3] N. Jayabalan, S. Nair, Z. Nuzhat, G.E. Rice, F.A. Zúñiga, L. Sobrevia, A. Leiva, C. Sanhueza, J.A. Gutiérrez, M. Lappas, D.J. Freeman, C. Salomón, Cross talk between
215 adipose tissue and placenta in obese and gestational diabetes mellitus pregnancies via exosomes, Front. Endocrinol. (Lausanne) 8 (2017) 239.

[4] American Diabetes Association (ADA), 2018. Standards of medical care in diabetes, 2018. Diabetes Care 41 (2018) S1–S159.

[5] World Health Organization (WHO), 2018. Obesity and overweight. Fact sheet 311.
220 World Health Organization, Geneva, Switzerland. http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (Accessed 20 August 2018).

[6] National Health Survey Report 2017, Ministry of Health, Gobierno de Chile. http://www.minsal.cl/wp-content/uploads/2017/11/ENS-2016-17_PRIMEROS-RESULTADOS.pdf

225 [7] E. Ziv, E. Shafir, *Psammomys obesus* (sand rat): Nutritionally induced NIDDM-like syndrome on a thrifty gene background, in: E. Shafir (Ed.), Lessons from Animal Diabetes, London, Smith-Gordon, 1995, pp. 285–300.

[8] S. Kalra, Diabesity, J. Pak. Med. Assoc. 63 (2913) 532–534.

[9] U. Campia, M. Tesauro, N. Di Daniele, C. Cardillo, The vascular endothelin system in obesity and type 2 diabetes: Pathophysiology and therapeutic implications, Life Sci. 118 (2014) 149–155.

[10] D.J. Hill, Placental control of metabolic adaptations in the mother for an optimal pregnancy outcome. What goes wrong in gestational diabetes? Placenta 2018. doi: 10.1016/j.placenta.2018.01.002

[11] R. Villalobos-Labra, L. Silva, M. Subiabre, J. Araos, R. Salsoso, B. Fuenzalida, T. Sáez, F. Toledo, M. González, C. Quezada, F. Pardo, D.I. Chiarello, A. Leiva, L. Sobrevia, Akt/mTOR role in human foetoplacental vascular insulin resistance in diseases of pregnancy. J. Diabetes Res. 2017 (2017), 1–13.

[12] M. Subiabre, L. Silva, F. Toledo, M. Paublo, M.A. López, M.P. Boric, L. Sobrevia, Insulin therapy and its consequences for the mother, foetus, and newborn in gestational diabetes mellitus. Biochim. Biophys. Acta - Mol. Basis Dis. 2018. https://doi.org/10.1016/j.bbadis.2018.06.005

[13] B. Kerr, A. Leiva, M. Farías, S. Contreras-Duarte, F. Toledo, F. Stolzenbach, L. Silva, L. Sobrevia, Foetoplacental epigenetic changes associated with maternal metabolic dysfunction, Placenta 2018. doi: 10.1016/j.placenta.2018.04.006

[14] F. Pardo, P. Arroyo, C. Salomón, F. Westermeier, R. Salsoso, T. Sáez, E. Guzmán-Gutiérrez, A. Leiva, L. Sobrevia, Role of equilibrative adenosine transporters and adenosine receptors as modulators of the human placental endothelium in gestational diabetes mellitus, Placenta 34 (2013) 1121–1127.

[15] F. Pardo, L. Silva, T. Sáez, R. Salsoso, J. Gutiérrez, C. Sanhueza, A. Leiva, L. Sobrevia, Human supraphysiological gestational weight gain and fetoplacental vascular dysfunction. Int. J. Obesity 39 (2015) 1264–1273.

[16] M. Subiabre, L. Silva, R. Villalobos-Labra, F. Toledo, M. Paublo, M.A. López, R. Salsoso, F. Pardo, A. Leiva A, L. Sobrevia, Maternal insulin therapy does not restore foetoplacental endothelial dysfunction in gestational diabetes mellitus. Biochim. Biophys. Acta – Mol. Basis Dis. 1863 (2017) 2987–2998.

[17] R. Villalobos-Labra, P.J. Sáez, M. Subiabre, L. Silva, F. Toledo, F. Westermeier, F. Pardo, M. Farías, L. Sobrevia, Pre-pregnancy maternal obesity associates with endoplasmic reticulum stress in human umbilical vein endothelium. Biochim. Biophys. Acta – Mol. Basis Dis. (2018). doi: 10.1016/j.bbadis.2018.07.007

[18] G.H. Moen, C. Sommer, R.B. Prasad, L. Sletner, L. Groop, E. Qvigstad, K.I. Birkeland, Mechanisms in endocrinology: epigenetic modifications and gestational diabetes: a systematic review of published literature, Eur. J. Endocrinol. 176 (2017) R247-eR267.

[19] A.B. Peixoto, L.C. Rolo, L.M.N. Nardozza, E. Araujo Jr., Epigenetics and preeclampsia: programming of future outcomes, Meth. Mol. Biol. 1710 (2018) 73e83.

[20] M.H. Schoots, S.J. Gordijn, S.A. Scherjon, H. van Goor, J.L. Hillebrands, Oxidative stress in placental pathology, Placenta (2018). doi: 10.1016/j.placenta.2018.03.003

[21] M.M. Faas, P. De Vos, Innate immune cells in the placental bed in healthy pregnancy and preeclampsia, Placenta (2018). doi: 10.1016/j.placenta.2018.04.012

[22] J. Gutiérrez, A. Aedo, J. Mora, J. Maldonado, R. Salsoso, F. Toledo, M. Farías, F. Pardo, A. Leiva, L Sobrevia, Preeclampsia associates with RECK-dependent decrease in human trophoblasts migration and invasion. Placenta 59 (2017) 19–29.

[23] N. Azevedo Portilho, M. Pelajo-Machado, Mechanism of hematopoiesis and vasculogenesis in mouse placenta, Placenta (2018). doi: 10.1016/j.placenta.2018.04.007

[24] D.I. Chiarello, R. Marín, F. Proverbio, P. Coronado, F. Toledo, R. Salsoso, J. Gutiérrez, L. Sobrevia, Mechanisms of the effect of magnesium salts in preeclampsia, Placenta (2018). doi: 10.1016/j.placenta.2018.04.011