Annals of Nutrition & Metabolism

Power of Programming - The placenta, maternal diet and adipose tissue development in the newborn

Journal:	*Annals of Nutrition and Metabolism*
Manuscript ID	Draft
mstype:	Review Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Symonds, Michael; The University of Nottingham, Child Health Bloor, Ian; The University of Nottingham, Child Health Ojha, Shalini; The University of Nottingham, Child Health Budge, Helen
Keyword:	Obesity, Reproduction/Pregnancy/Lactation, Infancy and Childhood

The placenta, maternal diet and adipose tissue development in the newborn

Michael E Symonds[1], Ian Bloor, Shalini Ojha and Helen Budge

Early Life Research Unit, Academic Division of Child Health, Obstetrics & Gynaecology, and [1]Nottingham Digestive Disease Centre and Biomedical Research Unit, School of Medicine, Queen's Medical Centre, The University of Nottingham, Nottingham NG7 2UH, United Kingdom

Corresponding author:
Professor Michael E. Symonds
Academic Division of Child Health Obstetrics & Gynaecology, School of Medicine, Queen's Medical Centre, The University of Nottingham, Nottingham NG7 2UH, United Kingdom

Phone: +44 1158230625 Fax: +44 1158230626.

Email: michael.symonds@nottingham.ac.uk

Abstract

Background:

A majority of adipose tissue present in the newborn possess the unique mitochondrial protein, uncoupling protein (UCP)1. It is thus highly metabolically active and capable of producing 300 times more heat per unit mass than any other organ in the body. The extent to which maternal obesity and/or an obesogenic diet impacts on placental function thereby resetting the relative distribution of different types of fat in the fetus is unknown.

Summary:

Developmentally the majority (if not all) fat in the fetus can be considered as classical brown fat, in which UCP1 is highly abundant. In contrast beige (or recruitable) fat which possess 90% less UCP1 may only appear after birth, as a majority of fat depots undergo a pronounced transformation that is usually accompanied by the loss of UCP1. The extent to which this process can be modulated in a depot specific manner and/or changes in the maternal metabolic environment remain unknown.

Key Messages:

An increased understanding of the mechanism by which offspring born to mothers possess excessive adipose tissue could enable sustainable interventions designed to promote the abundance of UCP1 possessing adipocytes. Ultimately thus would increase their energy expenditure and improving glucose homeostasis in these individuals.

The current challenge to public health with respect to the continued rise in the incidence of obesity around the world is widely considered to tackling maternal obesity [1]. This is largely due to epidemiologically based studies together with reviews indicating the potentially adverse effects of raised maternal body mass index (BMI) on pregnancy outcomes. The greater prevalence of obesity in pregnant women has occurred concurrently with an increase in gestational diabetes mellitus (GDM) [2] which can affect up to 14% of all pregnancies in the US, and around 2–6% of pregnancies in Europe [3, 4]. At the same time the plethora of reviews are largely based on gross measurements of outcomes such as birthweight and/or changes in BMI (body mass index) [5] that give comparatively little insight into body composition and/or metabolic regulation in those offspring. So although it is clear that women who are grossly obese are at greater risk of not completing a complication free pregnancy [6] whether this is the case for women who are overweight or moderately obese is less well established.

It should also be noted that in terms of the classification of being overweight, the BMI category for this has been lowered with time [7] thereby progressively raising the number of individuals included. At the same time it has been recognised that the relative risk of metabolic related disease is not simply related to BMI and can vary greatly depending on ethnicity, social class, age and gender. The extent to which the same classifications and their relationship with compromised metabolic health apply to women of reproductive age has yet to be established. Moreover, it appears that excessive weight gain through pregnancy may be of more concern than BMI per se [6]. In addition, interventions simply trying to reduce the incidence of large for gestational age (SGA) infants are likely to be unsuccessful as this is usually an arbitrary classification of the 10% of largest infants rather than an adverse health outcome. It is likely that a combination of raised fat mass together with enhanced postnatal and later fat growth will be necessary to result in the distinct phenotype that shows metabolic dysfunction in later life as well as predisposition to produce a similarly large and disproportionately sized infant.

In terms of interventions aimed at improving fetal outcomes with maternal obesity, given how unsuccessful these are in adults it is clear that we remain a long way off any clear or effective intervention. Indeed, for most dietary based interventions the usual success rate in terms of sustained wright loss over several years can be as low as 15%. The challenge in pregnant women is further amplified by the profound and quite rapid changes in metabolic regulation that occur in the mother from the time of conception and then through pregnancy. This occurs as her metabolism adapts to the dual demands of placenta-fetal growth and the neuro-endocrine adaptations that accompany pregnancy [8]. In the following brief review we will focus on the different critical windows of development and the potential interaction between placental and fetal adipose tissue growth, as high-lighted by others [9].

In most mammalian species relatively little adipose tissue is laid down in the fetus which may reflect the higher energetic costs of lipid accretion compared with carbohydrate and protein together the limited transfer of lipid across the placenta [10, 11]. The notable exception to this are humans in which significant quantaties of lipid can cross the placenta and the substantial amounts of fat present in term newborns, due in part to large amounts of subcutaneous fat [12]. This means that there is no obvious animal model for investigating their interaction and the extent to which modulating maternal diet at different stages of gestation impacts on both placental function and fetal adiposity [9]. It must also be noted that there are now three distinct types of fat i.e. brown, white and beige adipose tissue [10]. These may have different embryonic origins although this has yet to be confirmed in any species other than mice [13]. Furthermore the fetus is maintained within an hypoxic and thermally clamped environment which will further constrains adipose tissue growth [14]. It is possible that all fat laid down in the fetus for a majority of large mammalian species is primarily brown adipose tissue that is characterised as possessing the unique mitochondrial uncoupling protein (UCP1) [10]. The one exception being the pig which is litter bearing although brown fat has been found within an isolated depot [15]. When activated through the unmasking of GDP binding sites the free flow of protons across the mitochondria enables the rapid production of heat with the need for the production of ATP as required in mitochondria of all other tissues or organs [16]. This means that once maximally stimulated brown fat can produce up to 300 times more heat per unit mass than any other tissue in the body. The contribution of beige fat remains to be fully quantified as it contains around 10% of the amount of UCP1 as seen in classical brown fat. However, before it acquires this characteristic the adipose tissue precursors undergo a defined period of proliferation, and as such is located within a range of diverse depots in the fetus as summarised in Table 1.

Adipose tissue development and the modulation effect of maternal diet

The most abundant brown fat depot in humans is located within the supraclavicular (or neck) region and in contrast to most other depots is retained throughput the life cycle [17, 18]. Despite being first described fifty years ago [19] it is only very recently that a comparable depot has been found in any other species i.e. sheep [20]. The anatomical location is likely to be highly significant with respect to its functional role, given that brown fat has the capacity to ensure that the temperature of blood supplying the brain is maintained. This role will therefore not only be critical at birth but throughout the life cycle and could explain why acute stress, and the accompanying rise in cortisol stimulates heat production in supraclavicular brown fat [21]. In contrast, in rodents, at least, glucocorticoids inhibit brown fat function within the interscapular depot [22].

Given the recent discovery of significant amounts of brown fat in the neck region, currently there are no publications relating to the impact of changes in maternal diet on its growth and development pre or post-natally. In contrast, the peri-renal depot has been widely investigated and under conditions in which placental growth is modulated it shows a parallel response, possibly reflecting the changes in nutrient partitioning to the fetus [20]. Of particular interest is the finding that under conditions of increased food intake, although fetal growth is enhanced, relative fetal peri-renal fat mass are actually reduced, but the abundance of UCP1 is raised [23]. Surprisingly this type of model has not been further investigated as it would be expected to provide further insights into the impact of excess nutrient supply to the fetus and its impact of both pre and post-natal adiposity.

Future perspectives

Given the rediscovery of brown fat in humans and the acknowledgment that it is a vital organ implicated in metabolic regulation throughout the life cycle there is an urgent need for more studies on understanding its early development, especially in large mammals [24]. One approach currently being adopted is the use of large scale bioinformatics to describe and identify novel pathways. To date, this has only been undertaken on epicardial adipose tissue taken from neonates and infants that have undergone heart surgery [25]. These analyses have further revealed that the transition to infancy is a critical stage for changes in adipose tissue morphology, that is reflected by a unique pattern of gene expression that included a significant proportion of thermogenic gene transcripts (~10%). The patterns identified were specific for each developmental stage, and persisted even after the rebound in abundance of thermogenic genes in later childhood. Using weighted gene co-expression network analysis, precise anthropometric specific correlations with (corrected) postnatal growth were identified. These changes in gene expression pathways followed the decline of thermogenic capacity within the fat depot. Our results also indicated a sequential order of transcriptional events affecting cellular pathways that could potentially explain the variation in the amount or activity of BAT in adulthood. In summary, this type of experiment approach could provide a novel resource to elucidate gene regulatory mechanisms underlying the progressive development of adipose tissue through the life cycle.

References

1 Fitzsimons KJ, Modder J: Setting maternity care standards for women with obesity in pregnancy. Seminars in Fetal & Neonatal Medicine 2010;15:100-107.

2 Schafer-Graf U: The HAPO Study and its Consequences for the Diagnostic of Gestational diabetes. Geburtshilfe Und Frauenheilkunde 2009;69:259-261.

3 Dominguez LJ, Martinez-Gonzalez MA, Basterra-Gortari FJ, Gea A, Barbagallo M, Bes-Rastrollo M: Fast Food Consumption and Gestational Diabetes Incidence in the SUN Project. PloS one 2014;9:e106627.

4 Buckley BS, Harreiter J, Damm P, Corcoy R, Chico A, Simmons D, Vellinga A, Dunne F, Group DCI: Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. Diabetic medicine : a journal of the British Diabetic Association 2012;29:844-854.

5 Godfrey KM, Reynolds RM, Prescott SL, Nyirenda M, Jaddoe VW, Eriksson JG, Broekman BF: Influence of maternal obesity on the long-term health of offspring. Lancet Diabetes Endocrinol 2016

6 Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X: Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. PLoS One 2013;8:e61627.

7 Kuczmarski RJ, Flegal KM: Criteria for definition of overweight in transition: background and recommendations for the United States. Am J Clin Nutr 2000;72:1074-1081.

8 Ojha S, Fainberg HP, Sebert S, Budge H, Symonds ME: Maternal health and eating habits: metabolic consequences and impact on child health. Trends in molecular medicine 2015;21:126-133.

9 Wankhade UD, Thakali KM, Shankar K: Persistent influence of maternal obesity on offspring health: Mechanisms from animal models and clinical studies. Mol Cell Endocrinol 2016;435:7-19.

10 Symonds ME, Pope M, Budge H: The ontogeny of brown adipose tissue. Ann Rev Nutr 2015;35:295-320.

11 Symonds ME: Brown adipose tissue growth and development. Scientifica 2013;2013:14. http://dx.doi.org/10.1155/2013/305763.

12 Widdowson EM: Chemical composition of newly born animals. Nature 1950;116:626-628.

13 Cypess AM, Haft CR, Laughlin MR, Hu HH: Brown fat in humans: Consensus points and experimental guidelines. Cell Metab 2014;20:408-415.

14 Symonds ME, Bird JA, Clarke L, Gate JJ, Lomax MA: Nutrition, temperature and homeostasis during perinatal development. Exp Phys 1995;80:907-940.

15 Mostyn A, Attig L, Larcher T, Dou S, Chavatte-Palmer P, Boukthir M, Gertler A, Djiane J, Symonds ME, Abdennebi-Najar L: UCP1 is present in porcine adipose tissue and is responsive to postnatal leptin. J Endocrinol 2014;223:M31-38.

16 Cannon B, Nedergaard J: Brown adipose tissue: function and physiological significance. Phys Rev 2004;84:277-359.

17 Cypess AM, White AP, Vernochet C, Schulz TJ, Xue R, Sass CA, Huang TL, Roberts-Toler C, Weiner LS, Sze C, Chacko AT, Deschamps LN, Herder LM, Truchan N, Glasgow AL, Holman AR, Gavrila A, Hasselgren PO, Mori MA, Molla M, Tseng YH: Anatomical localization, gene expression profiling and functional characterization of adult human neck brown fat. Nat Med 2013;19:635-639.

18 Symonds ME, Henderson K, Elvidge L, Bosman C, Sharkey D, Perkins AC, Budge H: Thermal imaging to assess age-related changes of skin temperature within the supraclavicular region co-locating with brown adipose tissue in healthy children. J Pediatr 2012;161:892-898.

19 Aherne W, Hull D: Brown adipose tissue and heat production in the newborn infant. J Pathol Bacteriol 1966;91:223-234.

20 Symonds ME, Pope M, Sharkey D, Budge H: Adipose tissue and fetal programming. Diabetologia 2012;55:1597-1606.

21 Robinson LJ, Law JM, Symonds ME, Budge H: Brown adipose tissue activation as measured by infrared thermography by mild anticipatory psychological stress in lean healthy females. Exp Physiol 2016;101:549-557.

22 Ramage LE, Akyol M, Fletcher AM, Forsythe J, Nixon M, Carter RN, van Beek EJ, Morton NM, Walker BR, Stimson RH: Glucocorticoids Acutely Increase Brown Adipose Tissue Activity in Humans, Revealing Species-Specific Differences in UCP-1 Regulation. Cell Metab 2016;24:130-141.

23 Budge H, Bispham J, Dandrea J, Evans E, Heasman L, Ingleton PM, Sullivan C, Wilson V, Stephenson T, Symonds ME: Effect of maternal nutrition on brown adipose tissue and its prolactin receptor status in the fetal lamb. Pediatr Res 2000;47:781-786.

24 Aldiss P, Davies G, Woods R, Budge H, Sacks HS, Symonds ME: 'Browning' the cardiac and peri-vascular adipose tissues to modulate cardiovascular risk. Int J Cardiol 2016;228:265-274.

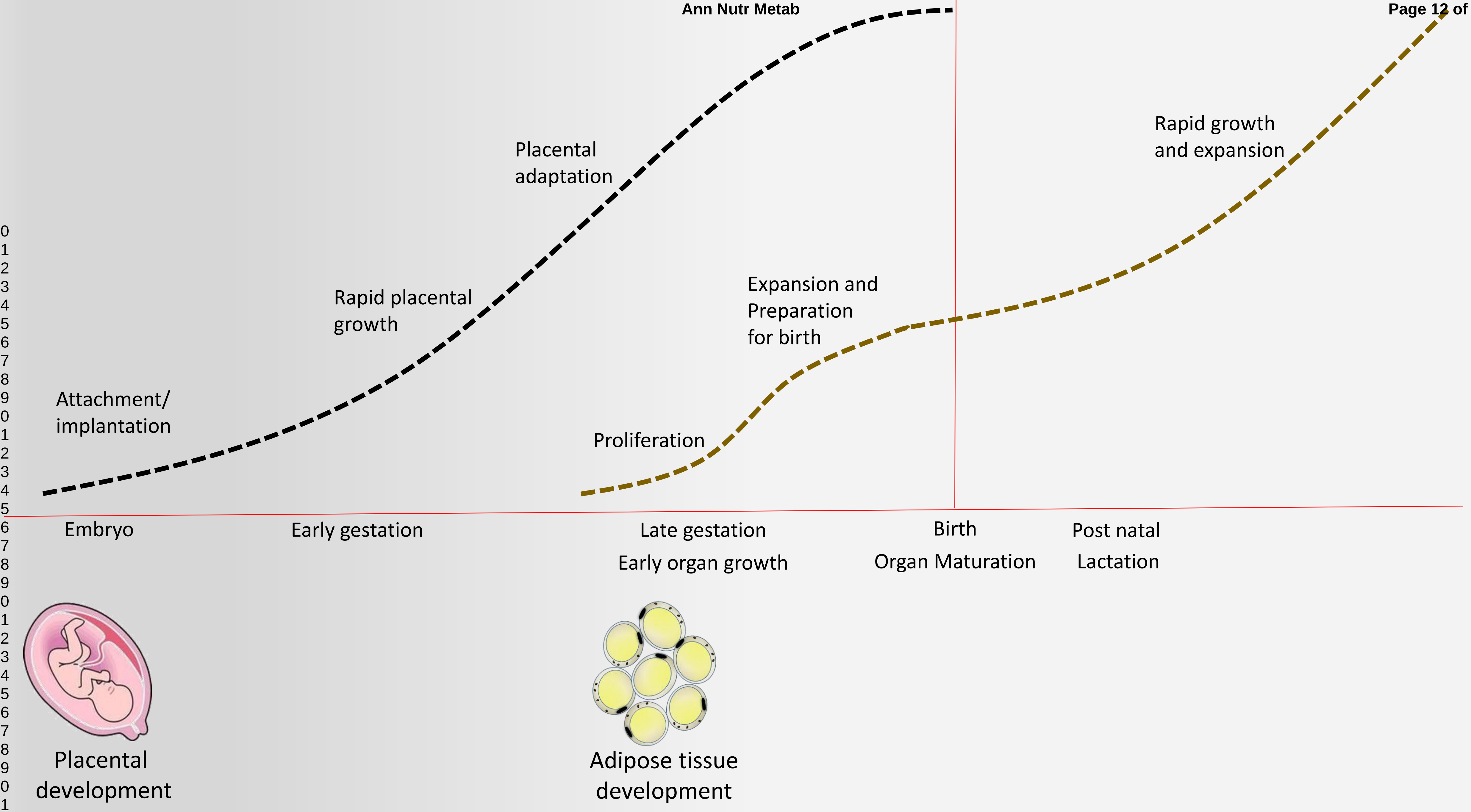
25 Ojha S, Fainberg HP, Wilson V, Pelella G, Castellanos M, May ST, Lotto AA, Sacks H, Symonds ME, Budge H: Gene pathway development in human epicardial adipose tissue during early life. JCI Insight 2016;1:e87460.

Figure Title

Figure 1. Summary of the developmental trajectories of the placenta and adipose tissue in large mammals.

Table 1. Summary of the main fat depots in the fetus and newborn that contain the brown adipose tissue specific uncoupling protein (UCP1).

Anatomical location	Description	Potential function	Nutritionally responsive in utero
Supraclvicular	Located in the neck region surrounding blood vessels	Maintaining the temperature of blood supplying the brain	Not known
Pericardial	Surrounds the heart	Maintaining heart temperature and preventing lipotoxicity	Responds to prevailing nutrient supply in late gestation
Epicardial	Along myocardium, beneath visceral pericardium and pericardial sac. Surrounds coronary arteries	Thermogenesis and related processes	Not known
Perirenal	Surrounds the kidney and adrenal glands	Thermogenesis	Reduced mass with suboptimal nutrition. Increased nutrition promotes UCP1 but not total fat mass


Attachment/
implantation
Rapid placental
growth
Placental
adaptation
Proliferation
Expansion and
Preparation
for birth
Rapid growth
and expansion
Embryo
Early gestation
Late gestation
Early organ growth
Birth
Organ Maturation
Post natal
Lactation
Placental
development
Adipose tissue
development