Review Article

Indian Journal of Maternal-Fetal and Neonatal Medicine
Volume 5 Number 1, January - June 2018
DOI: http://dx.doi.org/10.21088/ijmfnm.2347.999X.5118.15

Exploring Fetal Factors Affecting Fetal Growth: Review Series 1

Alka Patil[1], Radhika Bansal[2], Pankaj Pawar[3]

Author's Affiliation:
[1]Professor & HOD [2,3]Resident, Department of Obstetrics and Gynaecology, ACPM Medical College, Dhule, Maharshtra 424001, India.

Corresponding Author:
Alka Patil,
Prof & HOD, Department of Obstetrics and Gynaecology, ACPM Medical College, Dhule, Maharshtra 424001, India.
E-mail: alkabpatil@rediffmail.com

Received on 14 December 2017
Accepted on 19 January 2018

Abstract

Regulation of fetal growth is complex and still poorly understood. It involves genetic, nutritional, environmental, placental, hormonal and fetal factors. Weight of the child at birth is critical determinant of neonatal morbidity and mortality and the risk of metabolic diseases throughout the life span. Contributing fetal factors for low birth weight are multifaceted and include factors such as: maternal age, poor fetal genome, fetal infections, hormones, fetal malformations, multiple fetuses, amino acids, glucose, lipids. Risk factors for macrosomia are maternal diabetes, high pre- pregnancy BMI, excessive weight gain during pregnancy, multiparity, parental height, prolonged gestation. Nutritional insult during a critical period of gestation may leave permanent 'memory' throughout life. Early antenatal screening for chromosomal abnormalities and congenital malformations will ensure continuation of healthy pregnancy.

Keywords: Fetus; Low Birth Weight; Macrosomia; Genetic; Fetal Infections; Malformations.

Introduction

Being cared for, nurtured and supported has a much greater impact on the health of a mother and her child than the constant medical search for what might be 'wrong', where the basic assumption is that something must be, if only you search hard enough to find it. Maternal and fetal health is important for overall public health and it is possible to identify early signs or risk factors for atleast some of the major causes of ill- health. Those women at highest risk of problems (such as those with low education, low socioeconomic status , low residential stability, very young mothers) are also least likely to engage with intervention programmes [1].

Factors affecting fetal growth and development are [2]:

- Genetic control
- Environmental
- Nutritional
- Uteroplacental
- Fetal
- Cultural
- Socioeconomic

It is beyond the scope of this article to explore all the factors associated with fetal growth. In this review series 1, we will discuss fetal factors affecting fetal growth. Maternal, hormonal, nutritional and environmental factors will be appraised in next review series.

Growth is a dominant biological activity during the 9 months of prenatal life. Growth is an increase in the size of the body as a whole or the size attained by specific parts of the body. It is a fundamental characteristic of all living organisms. Growth is a form of motion. Growth means the increase in the size of the various parts and organs of the body by multiplication of cells and intercellular components during the period commencing from fertilization to physical maturity. During fetal stage the rate of growth in length as well as weight is considerably high.The regulation of fetal growth is complex and still very poorly understood. It involves genetic factors,

maternal nutrition and cardiovascular adaptations, placental growth and function, and to a certain extent fetal factors, including fetal hormones.

Significance of Birth Weight

The weight of a child at birth is a critical determinant of neonatal morbidity and mortality and the risk of metabolic diseases throughout the life span: growth retarded [intrauterine growth retardation/ small for gestational age (SGA)] infants are predisposed to hypoglycemia, hypocalcemia, hypothermia, asphyxia, and cognitive dysfunction[3]. LBW plays a direct or indirect role in more than 70% of infant mortalities[4]. Those who have rapid catch-up weight gain in early childhood are at increased risk for adult-onset type 2 diabetes, hypertension, preeclampsia, dyslipidemia, and ischemic heart disease [5].

The intrauterine environment of the conceptus may alter expression of the fetal genome and have lifelong consequences. This phenomenon is termed "fetal programming," which has led to the recent theory of "fetal origins of adult disease" [6]. Namely, alterations in fetal nutrition and endocrine status may result in developmental adaptations that permanently change the structure, physiology and metabolism of the offspring, thereby predisposing individuals to metabolic, endocrine, and cardiovascular diseases in adult life. Low birth weight (LBW) is an important determinant of childhood morbidity and mortality [7,8]. Child's birth weight is a significant factor which determines vulnerability for risk of childhood illnesses and childhood survival. Research highlights strong associations between LBW and increased risk of infections, malnutrition, poor academic performance and problems related to mental, behavior and learning difficulties during childhood [9,10].

Contributing factors for LBW are multifaceted and include factors such as:

- Maternal age,
- Poor maternal nutritional status, and non-pregnant weight,
- Gestational age,
- Intervals between pregnancies,
- Parity,
- Educational status,
- Violence during pregnancy,
- Lack of antenatal care (ANC) and very low socio-economic status [11,12,13,14].

In India, low body mass index (BMI), short stature, anemia and/or other micronutrient deficiencies are known to increase the risk of giving birth to a baby with LBW [13,14]. For example, low BMI is a reliable indicator for protein-energy malnutrition, which affects fetal growth during pregnancy [15].

Macrosomia

American College of Obstetricians and Gynecologists (ACOG) defined macrosomia as birth-weight over 4,000 g irrespective of gestational age or greater than the 90th percentile for gestational age after correcting for neonatal sex and ethnicity [16]. These births affect 3-15% of all pregnancies [17]. Macrosomia as well as the presence of a large fetus, either defined by a weight cutoff or as large for the gestational age in the literature, are associated with numerous perinatal and maternal complications [16,18,19].

Fetal macrosomia is common in obstetrics with problems to both the mother and the newborn. It has been associated with significant risk of morbidity and mortality. Over the years, the trend in fetal macrosomia has been shown to be increasing worldwide. Several risk factors have been identified in the causation of macrosomia. These include maternal diabetes, high pre- pregnancy Body Mass Index (BMI), excessive weight gain during pregnanacy, multiparity, male sex, parental height and prolonged gestation. During labour cephalo-pelvic disproportion can result in fetal distress and difficult deliveries are frequent in this group of infants. Maternal complications include increased risk of Caesarean section, postpartum haemorrhage and perineal lacerations. The risk increases with a higher birthweight of the infant. Neontal complications include birth asphyxia, birth trauma, and hypocalcemia are most often noted in infants born to diabetic mothers. Furthermore, these infants may be at a higher risk of obesity and diabetes later in life. Mothers should be screened using risk factors identified and be treated as a high risk delivery, with planned delivery and aftercare [20].

Early Stage of Fetal Growth

Because of small amount of yolk in human ovum, growth of the embryo-fetus is dependent on maternal nutrition during first 2 month. During first few days after implantation, blastocyst nutrition comes from intestinal fluid of endometrium and surrounding maternal tissues [21].

• *Human Fetal Growth: Sequential Patterns*

Human fetal growth is characterized by sequential patterns of [22]:

- Tissue and organ growth
- Differentiation
- Maturation
- Vulnerable Period of Fetal Growth:

Maternal undernutrition during gestation reduces placental and fetal growth of both domestic animals and humans [23,24]. Available evidence suggests that fetal growth is most vulnerable to maternal dietary deficiencies of nutrients (e.g., protein and micronutrients) during the peri-implantation period and the period of rapid placental development [25 -27].

Contributing Factors of Fetal Growth

• *Fetal Genetic Factors*

Normal intrauterine growth and development depend on the genetic potential of an individual, modulated by environmental factors including maternal healthand nutrition, and the endocrine environment. Miozzo and Simomi state that genes interact in a complex way to ensure fetal growth and that specific genes promoting fetal and placental growth can be altered in cases of impaired fetal development. The interaction between the genetic growth potential, the capability of the maternal-placental system to transfer nutrients to the fetus and the endocrine environment determine whether the fetus will follow its growth curve during intrauterine life modulated by environmental factors including: maternal health, nutrition and endocrinal environment [28].

• *Lipids and Fetal Growth*

Excessive transfer of lipids results in fetal overgrowth. Free fatty acids in maternal plasma may be transferred to the fetus via facilitated diffusion or after liberation of fatty acids from triglycerides by trophoblastic lipases. Maternal triglyceride levels are correlated wih birth weight in both early and late pregnancy [22].

• *Glucose and Fetal Growth*

Although dependent on the mother for nutrition , the fetus also actively participates in providing for its own nutrition. Glucose is the major nutrient for fetal growth and energy. Mechanisms exist during pregnancy to minimise maternal glucose use so that limited maternal supply is available to the fetus. Human placental lactogen (HPL), a hormone normally abundant in the mother but not in the fetus, blocks peripheral uptake and use of glucose, while promoting mobilization and use of free fatty acids by maternal tissues [21]

• *Fetal Adipokines*

Other hormones implicated in fetal growth are derived from adipose tissue known as adipokines, include leptin, the protein product of obesity gene. Fetal leptin concentration increase during gestation, and they correlate with birthweight. Other adipokines are:

- Adiponectin
- Ghrelin
- Follistatin
- Resistin
- Omentin
- Chemarin

Fetal growth is also dependent on adequate supply of nutrients [22].

• *Fetal Exposure to Glucocorticoids*

Fetal exposure to glucocorticoids has been associated with intrauterine growth restriction, impaired nephrogenesis, elevated blood pressure, altered fat metabolism, and insulin resistance in later life [29].

Micronutrient restriction may cause defects in developing organs. Severe micronutrient deficiencies or excesses can have teratogenic effects on the developing fetus. Moderate nutritional deficiencies or excesses during critical periods of fetal development may cause more subtle damage, potentially due to reduced tissue oxygenation as a result of anemia [30], increased oxidative stress [31], or impaired organ development. Maternal zinc restriction, for example, results in renal oxidative damage, as indicated by an increase in lipid peroxidation, reduction in glutathione levels, and glutathione peroxidase and catalase activities within the kidney [32].

• *Fetal Infections*

Fetal infections may occur at any time during gestation and their severity will vary depending on the virulence of the agent, the susceptibility and gestational age of the fetus, and the route of the infection. An infection can be transmitted from mother to the fetus in many ways. Transplacental transmission during embryonic and fetal development (prenatal) and the one occurring by direct contact between the fetus and maternal tissues duringthe delivery (perinatal transmission) represent the two commonest ways of interaction between the infectious agent and the fetus [33].

Viral, bacterial, protozoan and spirochetal infections have been implicated in up to 5 percent of fetal growth restriction cases [22]. Cytomegalovirus, rubella, toxoplasma gondii, plasmodium malariae and Treponema pallidum are associated to SGA unrelated to placental insufficiency. These pathogens lead to placental inflammation, lesions of the vascular endothelium and fetalviraemia, with direct inhibition of cellular multiplication, obliterating angiopathy, chromosome rupture and cytolysis. This group of SGA (a) is small since infected, (b) is usually asymmetrically small [34]. Amongst these pathogens best known are rubella and cytomegalovirus infection. Both promote calcifications in the fetus that are associated with cell death [22].

Tuberculosis and syphilis have both been associated with poor fetal growth. Both extrapulmonary and pulmonary tuberculosis have been linked with low birth weight. Adverse effects of tuberculosis on maternal health, compounded by effects of poor nutrition and poverty is important. Paradoxically, with syphilis, the placenta is almost always larger and heavier due to edema and perivascular inflammation. Congenital syphilis also strongly linked with preterm birth and low birth infants. Congenital malaria have also been associated with low birth weight [22].

IUGR can be seen if organism interferes at the time of cell division. These babies have decreased number of morphologically normal cells and result in symmetrical IUGR [35].

• *Fetal Chromosomal Anomalies*

Depending on which chromosome is redundant , there may be associated poor growth in fetuses with autosomal trisomies. For example, in trisomy 21, fetal-growth restriction is generally mild. By contrast, fetal growth in trisomy 18 is always significant. Growth failure has been documented as early as the first trimester using crown rump length. Aneuploidic patches in the placenta–confined placental mosaicism- can cause placental insufficiency which may account for many unexplained growth- restricted fetuses. Turner syndrome has been associated with a low embryo volume during first trimester sonography. This early finding manifests as growth restriction at delivery [22].

• *Multiple Fetuses*

Due to competition for nutrients, multiple fetuses resulting from assisted reproductive technologies are often at risk of undernutrition and therefore fetal growth restriction [36]. Thus, various nutritional and pathological conditions can result in IUGR.

Fetal growth is independent of the number of fetuses until approx. 30 weeks of gestation, after which growth of multiples gradually fall off compared with singletons. The mechanisms for IUGR in multiple gestations are [37] :

- Uterine crowding
- Limitation of pacental perfusion
- Anomalous umbilical cord insertion
- Infection
- Fetal anomalies
- Maternal complications
- Monochorionicity

Monochorionic twins are more likely than dichorionic twins to be IUGR.

• *Arginine*

Arginine a nutritionally essential amino acid for the fetus [38] plays a key role in development of the conceptus (embryo/fetus, associated placental membranes, and fetal fluids). Arginine is a common substrate for nitric oxide (NO) and polyamine syntheses via NO synthase (NOS) and ornithine decarboxylase (ODC) [38]. NO is a major endothelium-derived relaxing factor, and plays an important role in regulating placental-fetal blood flows and, thus, the transfer of nutrients and O_2 from mother to fetus [39]. Likewise, polyamines regulate DNA and protein synthesis, and therefore, cell proliferation and differentiation [38,40]. Thus, NO and polyamines are key regulators of angiogenesis (the formation of new blood vessels from preexisting vessels) and embryogenesis [41], as well as placental and fetal growth. IUGR in humans is associated with impaired whole body NO synthesis [42] and with decreases in arginine transport, eNOS activity, and NO synthesis in umbilical vein endothelial cells [43]. Maternal undernutrition and hypercholesterolemia during pregnancy (frequently occurring in obese subjects) have profound effects on the synthesis of NO and polyamines.

Discussion

Nutrition is the major intrauterine environmental factor that alters expression of the fetal genome and may have lifelong consequences. There is growing evidence that maternal nutritional status can alter the epigenetic state (stable alterations of gene

expression through DNA methylation and histone modifications) of the fetal genome. This may provide a molecular mechanism for the impact of maternal nutrition on both fetal programming and genomic imprinting. Promoting optimal nutrition will not only ensure optimal fetal development, but will also reduce the risk of chronic diseases in adults. Maternal nutrition plays a critical role in fetal growth and development [44].

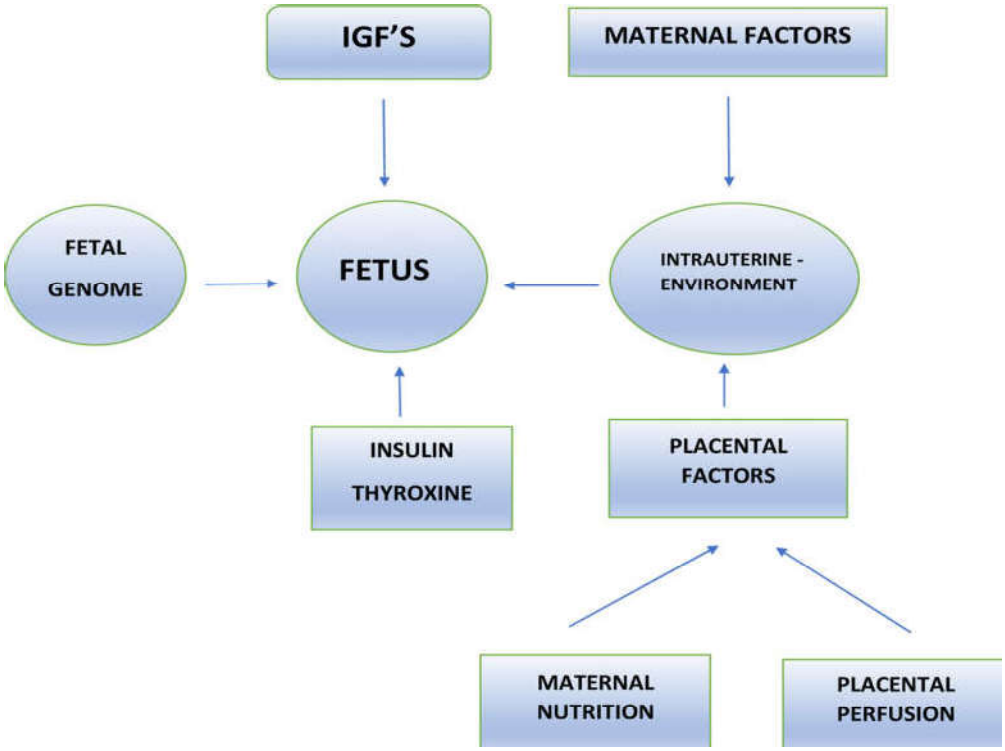
The crucial roles of the arginine-dependent metabolic pathways, intravenous or oral administration of arginine may provide a potentially novel solution to enhancing placental-fetal blood flows (and therefore transfer of nutrients and O_2 from mother to fetus), thereby improving fetal growth. Promoting an optimal intrauterine environment will not only ensure optimal fetal development, but will also reduce the risk of chronic diseases in adults [45,46].

Growth factors exert their effects via intracellular cascades that utilize common signalling molecules; many of which are dysregulated in fetal growth disorders. Therefore, enhancing the growth factor levels alone may not be sufficient to rescue the placental phenotype; instead, it is likely that greater therapeutic benefits may be achieved by targeting growth factor receptors, or indeed the downstream signaling molecules that are responsible for exerting their mitogenic effects [47].

Shoulder dystocia, brachial plexus injury, skeletal injuries, meconium aspiration, prenatal asphyxia, hypoglycemia, and fetal death are reported to be associated with macrosomia [48,50]. Maternal complications of macrosomia include prolonged labor, labor augmentation with oxytocin, cesarean delivery, postpartum hemorrhage, infection, 3rd and 4th-degree perineal tears, thromboembolic events, and anesthetic accidents [48,49]. Furthermore, macrosomic infants are at an increased risk of type 2 diabetes mellitus, hypertension, and obesity in adulthood [51].

Some studies have reported that excess weight gain during pregnancy is associated with macrosomia and other infant as well as maternal adverse outcomes [48,52,53,54] Gestational diabetes and fasting blood glucose are considered as the risk factors for macrosomia [49,55,56].

Gestational diabetes is the most important predictor of macrosomia births. Maternal obesity, increasing age, and parity are also considered as the main risk factors for fetal macrosomia. Gynecologist and newborns specialist are recommended to care more for the mothers with gestational diabetes and a



Laxmi Sheshadri, Gita Arjun,Pregestational and gestational diabetes mellitus, Laxmi Sheshadri, Gita Arjun, Essentials of obstetrics, Wolters Kluwer, New Delhi 2017 [58]

history of macrosomic births. Following this recommendation is helpful for preventing other complications which may occur in macrosomic newborns as well as mothers.

Fetus develops maternal bonding in intrauterine life. This bonding is healthier, secure and strengthened if preconception care is rendered to mother.In obstetrics, prevention is better than cure. Prevention of fetal growth disorders begins in preconception period.Preconception, conception, pregnancy, birth and childbearing are in continuum. Earlier events affect the present and future.Therefore, to ensure optimum fetal growth and development in intrauterine period, it is essential that mother enters pregnancy in a healthy state [57]. During preconception period only, she should be screened for infections which are detrimental to fetal growth. In pre conceptional period, maternal infections must be diagnosed and treated. During antenatal period, if maternal infection is detected, it should be eradicated. Early antenatal screening for chromosomal anomalies and congenital malformations will ensure continuation of healthy pregnanacy. Fetal surveillance will help to detect fetal growth disorders earlier. Etiological factors of these fetal growth disorders should be explored and definitive treatment must be given to pregnant woman.

Conclusion

Fetal growth depends upon various factors genetic, nutritional, environmental, uteroplacental and other fetal factors. Low birth weight baby can lead to a lot of financial stress in a family along with increased parental anxiety and depression. It can even influence professional and social life of mothers of those infants. Fetal macrosomia has been associated with neonatal and maternal morbidity. Hence prediction and early diagnosis of macrosomia are mainstay to achieve successful pregnancy outcome. Prevention of various fetal growth disorders and ensuring optimal fetal weight during pregnancy are essential in all healthy pregnancies.

Refrences

1. Vicki Williams; Antenatal care; AIMS Journal, 2013;25(4).
2. Dr Kaushik bose; Concept of human physical growth and development; Department of anthropology; vidyasagar university, Midnapore, west Bengal.
3. Murphy VE, Smith R, Giles WB, Clifton VL. Endocrine regulation of human fetalgrowth:the role of the mother, placenta, and fetus. EndocrRev 2006;27: 141–169.
4. Hosseini SM, Ghavami B, Salimzadeh H, et. al. Low birthweight and its relation to unwanted pregnancies; cohort study. J School Publ Health Inst Publ Health Res 2009;7(1):11-18. [In Persian].
5. Murphy VE, Smith R, Giles WB, Clifton VL. Endocrine regulation of human fetalgrowth:the role of the mother, placenta, and fetus. EndocrRev 2006;27: 141–169.
6. Barker, D.J.P. & Clark, P.M. Fetal undernutrition and disease in later life. Rev. Reprod. 1997;2:105-112.
7. Lawn JE, Cousens S, Zupan J. Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: When? Where? Why? Lancet. 2005;365:891–900. [PubMed: 15752534].
8. Alexander GR, Wingate MS, Bader D, Kogan MD. The increasing racial disparity in infant mortality rates: Composition and contributors to recent US trends. (e1-9).Am J Obstet Gynecol. 2008;198:51. [PubMed: 17870043].
9. Berkowitz GS, Papiernik E. Epidemiology of preterm birth. Epidemiol Rev. 1993;15:414–43. [PubMed: 8174665].
10. Dunin-Wasowicz D, Rowecka-Trzebicka K, Milewska-Bobula B, Kassur-Siemienska B, Bauer A, Idzik M, et. al. Risk factors for cerebral palsy in very low-birthweight infants in the 1980s and 1990s. J Child Neurol. 2000;15:417–20. [PubMed: 10868787].
11. Valero De Bernabe J, Soriano T, Albaladejo R, Juarranz M, Calle ME, Martinez D, et. al. Risk factors for low birth weight: A review. Eur J Obstet Gynecol Reprod Biol. 2004;116:3–15. [PubMed: 15294360].
12. Som S, Jr, Pal M, Adak DK, Gharami AK, Bharati S, Bharati P. Effect of socio-economic and biological variables on birth weight in Madhya Pradesh. Malays J Nutr. 2004;10:159–71. [PubMed: 22691737].
13. Ohlsson A, Shah P. Edmonton: Institute of Health Economics (IHE); Determinants and prevention of low birth weight: A synopsis of the evidence. 2008.
14. Schieve LA, Cogswell ME, Scanlon KS, Perry G, Ferre C, Blackmore-Prince C, et. al. The NMIHS Collaborative Study Group. Prepregnancy body mass index and pregnancy weight gain: Associations with preterm delivery. Obstet Gynecol. 2000;96:194–200. [PubMed: 10908762].
15. Elshibly EM, Schmalisch G. The effect of maternal anthropometric characteristics and social factors on gestational age and birth weight in Sudanese newborn infants. BMC Public Health. 2008;8:244. [PMCID: PMC2522375] [PubMed: 18638377].
16. Ng SK, Olog A, Spinks AB, Cameron CM, Searle J, Mc Clure RJ. Risk factors and obstetric complications of large for gestational age births with adjustments for community effects: Results from a new cohort study. BMC Public Health. 2010;10:460. [PMC free article] [PubMed].

17. Asplund CA, Seehusen DA, Callahan TL, Olsen C. Percentage change in antenatal body mass index as a predictor of neonatal macrosomia. Ann Fam Med. 2008;6:550–4. [PMC free article] [PubMed].

18. Kerényi Z, Tamás G, Kivimäki M, Péterfalvi A, Madarász E, Bosnyák Z, et al. Maternal glycemia and risk of large-for-gestational-age babies in a population-based screening. Diabetes Care. 2009;32: 2200–5. [PMC free article] [PubMed].

19. Abolfazl M, Hamidreza TS, Narges MY. Gestational diabetes and its association with unpleasant outcomes of pregnancy. Pak J Med Sci. 2008;24:566–70.

20. -Aisha salim said and Karim Premji Manji; Risk factors and outcomes of fetal macrosomia in a tertiary centre in Tanzania: a case- control study.

21. Cunningham, Lenovo, Bloom, Spong, Dashe, Hoffman, Casey, Sheffield; Embryogenesis and Fetal morphological development chapter 7; Williams obstetrics 24th edition, Mc Graw Hill Education, Newyork.

22. Cunningham, Lenovo, Bloom, Spong, Dashe, Hoffman, Casey, Sheffield; Fetal growth disorders chapter 44; Williams obstetrics 24th edition, Mc Graw Hill Education, Newyork.

23. Bell, A.W. & Ehrhardt, R.A. Regulation of placental nutrient transport and implications for fetal growth. Nutr. Res. Rev. 2002;15:211-30.

24. Barker, D.J.P. & Clark, P.M. Fetal undernutrition and disease in later life. Rev. Reprod. 1997;2:105-12.

25. Wu, G., Pond, W. G., Flynn, S. P., Ott, T. L. & Bazer, F. W. Maternal dietary protein deficiency decreases nitric oxide synthase and ornithine decarboxylase activities in placenta and endometrium of pigs during early ges-tation. J. Nutr. 1998;128:2395-02.

26. Sugden, M.C. & Holness, M.J. Gender-specific programming of insulin secretion and action. J. Endocrinol. 2002;175:757-767.

27. Waterland, R.A. & Jirtle, R.L. Early nutrition, epigenetic changes at transposons and imprinted genes, and enhanced susceptibility to adult chronic diseases. Nutrition 2004;20:63-68.

28. I. Cetin, V. Cozzi and P. Antonazzo; Fetal development after assisted reproduction; Placenta 2003;24: S104-S113.

29. Seckl JR, Meaney MJ. Glucocorticoid programming. Ann N Y Acad Sci. 2004;1032:63-84.

30. Crowe C, Dandekar P, Fox M, Dhingra K, Bennet L, Hanson MA. The effects of anaemia on heart, placenta and body weight, and blood pressure in fetal and neonatal rats. J Physiol. 1995;488:515-9.

31. Cambonie G, Comte B, Yzydorczyk C, Ntimbane T, Germain N, Le NL, Pladys P, Gauthier C, Lahaie I, et al. Antenatal antioxidant prevents adult hypertension, vascular dysfunction, and microvascular rarefaction associated with in utero exposure to a low-protein diet. Am J PhysiolRegulIntegr Comp Physiol. 2007;292:R1236-45.

32. Tomat AL, Inserra F, Veiras L, Vallone MC, Balaszczuk AM, Costa MA, Arranz C. Moderate zinc restriction during fetal and postnatal growth of rats: effects on adult arterial blood pressure and kidney. Am J PhysiolRegulIntegr Comp Physiol. 2008;295:R543-9.

33. Amarnath Bhide, SabaratnamArulkumaran, Kaizad R. Damania, Shirish N. Daftary, Arias' chapter 4, Fetalinfections, pg no. 51,52, Arias' Practical Guide to High-Risk Pregnancy and Delivery, 2015, ELSEVIER pvt ltd, India.

34. Amarnath Bhide, SabaratnamArulkumaran, Kaizad R. Damania, Shirish N. Daftary, Arias' chapter 5, fetal growth restriction, pg no. 88,89,91 Arias' Practical Guide to High-Risk Pregnancy and Delivery, 2015, ELSEVIER pvt ltd, India.

35. Varsha L. Deshmukh, Kana D Yelikar, Shreyas S. Patil. Fetal infections leading to congenitalmal formations, IJMFNM, 2014 Jul-Dec;1(2):105-13.

36. Marsal, K. Intrauterine growth restriction. Curr. Opin. Obstet. Gynecol. 2002;14:127-135.

37. Deshmukh Laxmikant S, Deshmukh Varsha. Neonatal outcome and management in twin gestation, IJMFNM, 2014 Jul-Dec;1(2):97-104.

38. Flynn, N. E., Meininger, C. J., Haynes, T. E. & Wu, G. The metabolic basis of arginine nutrition and pharma -cotherapy. Biomed. Pharmacother. 2002;56:427-38.

39. Bird, I.M., Zhang, L.B. & Magness, R.R. Possible mechanisms underlying pregnancy-induced changes in uterine artery endothelial function. Am. J. Physiol. 2003;284:R245-R258.

40. Ishida, M., Hiramatsu, Y., Masuyama, H., Mizutani, Y. & Kudo, T. Inhibition of placental ornithine decarboxylase by DL—difluoro-methyl ornithine causes fetal growth restriction in rat. Life Sci. 2002;70: 1395-1405.

41. Reynolds, L.P. &Redmer, D.A. Angiogenesis in the placenta. Biol. Reprod. 2001;64:1033-1040.

42. Hata, T., Hashimoto, M., Manabe, A., Aoki, S., Iida, K., Masumura, S. & Miyazaki, K. Maternal and fetal nitric oxide synthesis is decreased in pregnancies with small for gestational age infants. Human Reprod. 1998;13:1070-73.

43. Casanello, P. & Sobrevia, L. Intrauterine growth retardation is associated with reduced activity and expression of the cationic amino acid transport system y( )hCAT-1 and Y( )/hCAT-2B and lower activity of nitric oxide synthase in human umbilical vein endothelial cells. Circ. Res. 2002;91:127-134.

44. Guoyao Wu, Fuller W. Bazer, Timothy A. Cudd, Cynthia J. Meininger and Thomas E. Spencer; Maternal nutrition and fetal development; The journal of Nutrition ,Recent advances in nutritional sciences; J.Nutr. 2004;134: 2169-72.

45. Sugden, M.C. &Holness, M.J. Gender-specific programming of insulin secretion and action. J. Endocrinol. 2002;175:757-67.

46. Waterland, R.A. &Jirtle, R.L. Early nutrition, epigenetic changes at transposons and imprinted genes, and enhanced susceptibility to adult chronic diseases. Nutrition 2004;20:63-68.

47. Karen Forbes and Melissa Westwood. Maternal growth factor regulation of human placental development and fetal growth; Journal of endocrinology 2010;207:1-16.

48. Asplund CA, Seehusen DA, Callahan TL, Olsen C. Percentage change in antenatal body mass index as a predictor of neonatal macrosomia. Ann Fam Med. 2008;6:550–4. [PMC free article] [PubMed].

49. Abolfazl M, Hamidreza TS, Narges MY. Gestational diabetes and its association with unpleasant outcomes of pregnancy. Pak J Med Sci. 2008;24:566–70.

50. Ahmed SR, Ellah MA, Mohamed OA, Eid HM. Prepregnancy obesity and pregnancy outcome. Int J Health Sci (Qassim) 2009;3:203–8. [PMC free article] [PubMed].

51. Hermann GM, Dallas LM, Haskell SE, Roghair RD. Neonatal macrosomia is an independent risk factor for adult metabolic syndrome. Neonatology. 2010;98:238–44. [PMC free article] [PubMed].

52. Viswanathan M, Siega-Riz AM, Moos MK, Deierlein A, Mumford S, Knaack J, et. al. Outcomes of maternal weight gain. Evid Rep Technol Assess (Full Rep) 2008;1:1–223. [PMC free article] [PubMed].

53. Ouzounian JG, Hernandez GD, Korst LM, Montoro MM, Battista LR, Walden CL, et al. Pre-pregnancy weight and excess weight gain are risk factors for macrosomia in women with gestational diabetes. J Perinatol. 2011;31:717–21. [PubMed].

54. Zonana-Nacach A, Baldenebro-Preciado R, Ruiz-Dorado MA. The effect of gestational weight gain on maternal and neonatal outcomes. SaludPublica Mex. 2010;52:220–5. [PubMed].

55. Levy A, Wiznitzer A, Holcberg G, Mazor M, Sheiner E. Family history of diabetes mellitus as an independent risk factor for macrosomia and cesarean delivery. J MaternFetal Neonatal Med. 2010;23:148–52. [PubMed].

56. Tabatabaee SH, Mohammadbeigi A, Yazdani M, Zeighami B, Mohammadsalehi N. Gestational diabetes risk factors modeling in pregnant women. Int J Diab Dev Ctries. 2007;27:11–3.

57. Alka B. Patil, Lavanya Anuranjani, Amruta Ahirrao. Preconceptional care for chronic medical conditions, Indian journal of maternal, fetal and neonatal medicine. 2014 January - June;1(1): 31-39

58. Laxmi Sheshadri, Gita Arjun, Pregestational and gestational diabetes mellitus, Laxmi Sheshadri, Gita Arjun, Essentials of obstetrics, Wolters Kluwer, New Delhi 2017.