Biological perspectives on fetal growth up to the second trimester:

Introduction:

Most believe the beginning of an individual human life to occur at the later stages of pregnancy while some believe embryo to be a fully human person and like a citizen having every right. Thus killing a recently fertilized embryo is considered to be a murder by many religious groups. (1,2) The embryo from its beginning is cellular and alive but the question stays that being cellular does the embryo attains a full adult life. Religious groups often believe that when the body meets with the soul it becomes a living human being with all the basic rights but that entrapment of soul within the body does not determine the exact gestational age at which the ensoulment starts and is still questionable.

However, religious groups do make a difference between the moral status of the unformed and formed embryo as for many centuries, termination of pregnancy at an early stage carried death penalties than at a later stage.

From the medical point of view, the function of the brain is fundamentally linked to being a human as it controls more or less all the organs of the body. (3) Goldenring postulated that the 8- week mark as the starting point of life as he indicated in his view that at 8 weeks, there is an integration of the brain which is important for the viability of a personal human life. (4) Kushner argues that the start of life can be taken once the initiation of brain activity happens. (5) It is further stated that life starts when the whole organs after their development start to function as a whole under the direct guidance of the brain at 8 weeks of gestation. (6) Therefore at 8 weeks, can we really call it a brain which initiates life is still highly debatable.

Growth and dynamics of the fetal tissue during the first two semesters:

The gestation period is generally estimated in weeks and from the first day of the last menstrual period before conception. Therefore, the conceptual age and the period of actual embryonic and fetal growth may be 1 to 3 weeks less than the estimated gestational age of the fetus. Different centile charts have been developed globally to ascertain the fetal measurements to gestational age. (7,8) During the time of pregnancy, nutrition is an extremely important criterion for both the mother and the fetus as the nutritional status of the mother plays a significant role in shaping up the fetal growth. (9) Maximum development of the fetus is normally observed in the last 3rd trimester between 32 to 38 weeks as the fet6al growth reaches the peak by the 39th week. Normal full-term gestation is normally considered between 37 and 41 weeks. If born before 37 gestation weeks, it is normally termed as the premature baby or post 41 weeks then as the post matured baby. Growth, in essence, is a highly complex and dynamic process where nutrition in the initial blastocyst stage is derived from the fetal trophoblast whereas in the case of third fetal phase, due to the decrease in the trophoblastic activity nutrition is derived from diffusion from the maternal blood stream. (10) EM Widdowson described that the initial division of the fertilized ovum is not accompanied by an increase in its size for a few further divisions as the cells become progressively smaller with no total increase in the size. On the 9th day of implantation of the blastocyst post fertilization, synthesis of proteins from the amino acids, water, and inorganic substances makes the cells look large with an alteration in the cell division timing also with the immature organs showing a large percentage of extracellular fluid within it. (11)

In the first 2 to 3 weeks of fetal development, growth place is accompanied by cell division with differentiation of the organs and tissues where the cell division slows down with the increase in the size of the cell. Also, the extracellular fluid content decreases which are quite common during the fetal and early postnatal life. (12) Post birth, the rate of development of the different organs like heart, kidneys, lungs and liver tend to grow parallel to the body with the growth of spleen remains

the same between 26 weeks of gestation up to 13 weeks post birth. P Gruenwald, HN Main, and E Boyd showed that growth of the organs is maximum and rapid during childhood and adolescence than compared with before term. (13, 14) In the rat, the maximum rate of DNA synthesis is achieved at around 10 days of age.

Further EM Widdowson in 1972, observed that the total DNA in the human fetal liver increased rapidly from 15 weeks until term and the ratio of protein to DNA was virtually unchanged between 15 to 25 weeks thereby suggesting the increase in the cell number rather than the cell size during the early fetal stages. (9)Some lipid components like dipso phosphoinositide, sphingomyelin, cerebrosides etc also remain absent in the early stages of fetal development and appear only during the later fetal stages extending up to postnatal life. (15)

The first two semesters which are a total period of 6 months are extremely important and unique as far as the micro and macro environment are considered. (16) During this period, the fetus have special wound healing characteristics without the formation of fibrosis or scar and a delicate balance between matrix metalloproteinases (MMP's) and its tissue inhibitors or TIMP's with a lack of fibroplasia and increased expression of hyaluronidases and homeobox genes like HOXB13 and PAX 2. (17, 18, 19)

The head approximately constitutes a prominent part of the fetus and by the beginning of the 9th week and by the end of 12th-week rapid growth in the body length occurs along with primary ossification occurring in the cranium and long bones. (20) This ossification remains active in the early part of the second trimester and can be easily visible by USG at the beginning of the 16th week along with slow eye movement in the 14th week. Also, scalp hair patterning is observed during this period. (16)During the later half of the first and early second trimester, the growth of the head slows down. (21) The head becomes relatively small by 16 weeks time.

The gross morphology of the fetus during this 9th to 12th week further reveals the development of the upper limbs more rapidly compared to the lower limbs and the external genitalia is hard to distinguish between the male and female b y the end of 9th week and by 12-14th week the fetal genitalia can be recognized. Most of the matured fetal anatomy form, therefore, takes its shape and development during the onset of the 12th week. Intestines return to the abdomen y the 11th week, erythropoiesis in the liver starts at 9 weeks and by the end of 12 weeks the site of erythropoiesis shifts to the spleen. (22) Urine formation first appears between 9th and 12th week and urine is discharged via the urethra into the amniotic fluid which is again reabsorbed by the fetus after swallowing it. Through the placental membrane, the fetal waste products are transferred into the maternal circulation. (19) Intestinal coils can be observed clearly at the proximal end of the umbilical cord until the middle of the tenth week. (19)

13 to 16 weeks also accompanies a fast and rapid growth of the fetus with the lengthening of the lower limbs and its first movement which normally occurs at the end of the embryonic period and becomes coordinated by the 14th week but are too superficial to be felt by the mother. (19, 23) Also during this period is the positioning of the external ears on the lateral sides of the head,

The growth rate, however, slows down during the 17th to 24th week but the fetal growth still increases by 50 mm approximately and the fetal movements or quickening can be felt by the mother. (24) The fetal skin gets covered with a greasy, cheese-like substance also termed as vernix caseosa which consists of dead epidermal cells and a fatty substance or secretion from the fetal sebaceous glands. Lanugo is the fetal hair which helps to hold the vernix caseosa on the skin. (25) The female fetal uterus is formed by 18 weeks along with canalization of the vagina with many primordial ovarian follicles containing oogonia. In 20 weeks time, the testes of the male fetus begin to descend and are still located on the posterior abdominal wall as the ovaries in a case of the female fetus. (19) Fetal movements can be felt by the mother

Development of the Placenta and the fetomaternal barrier during the first two trimesters:

After two cell stage, series of cleavage produces the morula surrounded by the zona pellucida and an inner cell mass surrounded by the trophoblast layer which forms the trophectoderm and gives rise to the placenta. The inner cell mass gives rise to the embryo proper. The trophoblastic cells become more flat like and the inner cell mass gets attached to the inner side of the trophoblastic layer on one side also known as the Animal pole. The opposite side is known as the embryonic pole and this stage is often referred to as the blastocyst. (26) This implantation of the blastocyst on the Endometrium layer gives rise to the placenta in later stages. Chorion is formed from the trophoblasts. After implantation, the trophoblastic layer undergoes a series of cell division and forms bi-layered trophoblasts composed of multinucleated outer bi-layered syncytiotrophoblast and an inner Mononucleated cytotrophoblast layer. (27) The primary villis are formed from the cytotrophoblast layer and lacunae or spaces are formed from the intervillous space where there is a rich flow of maternal blood thereby marking the beginning of placentation. After 8 to 9 days post-fertilization, morphological changes occur in the inner cell mass forming the epiblast and the hypoblast.The epiblast which contains the amniotic epithelium gives rise to the three germ layers and the cells from the hypoblast migrate to form the yolk sac. (28)

The syncytiotrophoblast layer is a continuous layer extending on the entire surface of the villi and in the presence of tertiary villi an establishment of the intraplacental fetal circulation starts. However, there is no mixing of the maternal and the fetal blood in the initial stages of development due to the presence of the feto-maternal barrier which is made of 5 layers. The first layer being the continuous syncytiotrophoblast layer covering the villi and thus lining the intervillous spaces followed by the cytotrophoblast layer which is consistent in its appearance in the first trimester but later discontinuous in the second trimester. [29] The next two layers are the trophoblastic laminal layer and the connective tissue layer which is derived from the extraembryonic mesoderm followed by the final layer fetal endothelium layer which remains uncovered during the first and second trimester. With an increase in gestational time, the fetomaternal barrier undergoes structural changes like the thickness of the syncytiotrophoblast layer decreases from 15 μm to a mere 4.1 μm in the third trimester.

In the first trimester inhibition of the macrophages to the fetal compartment is inhibited by the presence of the placental barrier consisting of the cytotrophoblast, syncytiotrophoblast, and the villous mesenchymal layer. The cytotrophoblast layer disappears from the villus wall thereby decreasing the size of the barrier with increased vascularization in the second trimester and fetal vessels.(30) The presence of chorionic plate, intervillous space surrounding the chorionic villi, cell islands, basal plate from which the septa protrudes into the anchoring villi are observed in the first trimester. At the beginning of the eighth week, mesenchymal villi start developing.

The placenta, unlike the first trimester, has very well defined stages of layers in the second trimester. From day 32 to week 25, angiogenesis starts and by the end of the first trimester between 8-12th week, the maternal blood via the developing fetomaternal passage enters and floods the placental intervillous spaces without mixing with fetal blood. [31, 32, 33, 34] In and around 25 days, the presence of vascular endothelial growth factor (VEGF) and Placental growth (PGF) factors in the maternal plasma normally remains high and this continues till the second trimester [35, 36]. In the presence of angiogenesis and a relatively hypoxic environment, the trophoblast cells increase their proliferation and forms the highly vascularized villi which and eventually develops into a complex network of blood vessels and arteries later on and also helping in the commencement of exchange of nutrients, gases, oxygenated and deoxygenated blood. [37, 38, 39] Different types of

mechanisms are present by which feto-maternal exchange takes place like simple diffusion where mainly gaseous substances like oxygen, carbon dioxide, and fatty acids get exchanged. Active transport includes the passage of Iron, Calcium, and Iodine and by facilitated diffusion, glucose is transported.

Transportation of amino acids is facilitated by the secondary active transport system and water via bulk transport mechanism. However, taking the advantage of the above methods of transportation, harmful chemicals like cocaine, alcohol, nicotine, and sedatives can pass through the mother to the fetus thereby causing grave injuries to the fetal growth and development. Fick's Law usually governs the fetomaternal exchange and is as follows $Q/T = K \times A(Cm-Ct)/D$ where Q/T is defined as the rate of diffusion, K is the diffusion coefficient, A is the area of the membrane, D is the thickness of the membrane and (Cm-Ct) is the concentration gradient. (29) P-glycoprotein is highly expressed in the human and mouse syncytiotrophoblast layer forming the essential part of the placental barrier thereby playing an essential role in inhibiting the exchange or passage of drugs and other harmful and toxic substances to the fetus. [40, 41, 42]. The size of the fetomaternal barrier further reduces from 20-30 micrometers to 2-5 micrometers in the second trimester. However, in the first 10 weeks of development due to organogenesis, there is a lack of fetomaternal circulation. Hence if any toxic substance via the intercellular spaces enters the fetus, there is a high chance of embryonal toxicity as the fetal still do not have a complete structural and functional metabolic and excretion system present. The presence of Multidrug resistance protein 3 on the basolateral junction of the syncytiotrophoblast plasmalemma and in the villi endothelial cells of the capillaries helps in the elimination or efflux of these toxic substances. The presence of these transporters has shown to increase with an increase in the gestational time. From an immune point of view, trophoblastic cells fail to express MHC Class I and II molecules with the down-regulation of maternal NK cells by the expression of the nonclassical MHC genes. (43, 44) Further expression of the complement proteins and CD46, CD55 and CD59 on the surface of the trophoblasts layer helps in protecting the embryo in the first trimester. (45, 46)

The mucosal secretory immune system or SIS helps in imparting immune protection of the organs and two such types of secretory immune system (SIS) have been suggested to be present at the border between maternal and embryonic tissues [47, 48]. It acts as a barrier between the external and the internal environment for the organ [49, 50] Also, during the first trimester at around 4th week, presence of secretory components or SC and J chains remain in an up-regulated state, in the absence of the fetal lymphoid system and helps in functioning as a pathological barrier against the entry of foreign antigens to the fetal compartment.

Biochemical, molecular and structural developments in the human fetal brain in the initial stages:

At 8 weeks of gestation, the cerebral cortex is an extremely rudimentary structure. The cerebral cortex is further developed into neocortex which is a 6 layered structure and forms the bulk of the cerebral cortex structure and the rest is known as the allocortex or other cortex with elementary structures and 3 basic layers composed of the olfactory cortex and hippocampal formation. (51, 52, 53, 54) The neocortex undergoes a prolonged phase of differentiation, maturation, and the neocortical birth can be located after the 24th week of gestation i.e. when cortical reorganization starts and resembles the adult type. (55) Until 22-24 weeks of gestation, there is no presence of synapses in the cortical plates although there is a continuous influx of new neurons. Therefore neocortical birth can be assumed to be started after the 24th week of gestation. (56) The first part of the cerebral cortex to undergo differentiation is the hippocampal region of the allocortex area from the eighth week onwards and by 13th week it forms the circular strip on the medial and inferior aspects of the hemisphere. (57, 58, 59) Olfactory cortex initially appears to occupy a large part of the basal part of the brain, whereas, with later fetal development, the olfactory cortex becomes smaller and occupies only a small part of the brain. Hippocampus then becomes the main part of the adult allocortex. (60, 61) Hippocampal sulci are the earliest sulci which can be identified by fetal MRI at around 8 weeks of gestation.(62) Hippocampal primordial can be observed during the 9th week of

gestation developing from the cerebral hemisphere. (63) Adult hippocampal formation initiated by the 13th week of development and most pyramidal cells are generated by this time. (64) This period also observes an increase in the volume of the hippocampal formation and most pyramidal cells already formed undergoes the process of differentiation and the cellular components that are mainly formed are of glial in origin. (1) Reciprocal entorhinal-hippocampal projections are the first cortico-cortical connections established in the human brain. (65) This hippocampal differentiation formation in the allocortex of the brain is accompanied by intense expression of functional proteins in these areas. (66, 67, 68, 69) Therefore a 3 layered hippocampus structure is formed around the 13th week. (58, 59) This hippocampus formation plays major roles in memory and emotion, a comparator of a novel, and familiar stimuli, initiation and inhibition of behavioral strategies and therefore becomes a link to emotions such as anxiety, self-awareness and setting appropriate motor responses. Therefore this development of hippocampus can mark the onset of emotion, personhood, and memory, therefore, hypothesizes a hippocampal birth theory where personhood or an independent life cannot begin without its development. Also, on the lines of hippocampal development at the 13th gestational week, the vomeronasal organ or the VNO found in the nasal cavity have the connection with the brain development between the 12th and 14th weeks of human development. The VNO is an organ filled with fluid, the tubular structure located at the base of the nasal cavity via a duct at its anterior end. (1) It has direct axonal connections to the olfactory bulb and is a chemoreceptive structure. (70) Pheromones binds to these VNO structures and exerts behavioral and physiological responses thereby allowing chemical recognition of senses and communication. In humans, VNO is first detected at the 8th week of gestation, matures at 12th -14th week of development and becomes rudimentary before birth along with the VNO nerve associated ganglion cells. (71, 72) After 14th weeks of development, VNO loses receptor cells and becomes a ciliated pseudostratified epithelium. (73, 74) Also, the VNO connection degenerates between 14-28 weeks, therefore, making its function unclear. (75).

In the rat, the proliferation of the brain begins in about 7th gestational day. The proliferation of cells from the primitive ventricular zone of the brains starts from the 11th day and proceeds very rapidly producing a rapid number of cells in a few days. (76) Malnutrition, during this stage, can have a direct effect on the proliferation of the brain cells as measured by the DNA content of the brain. (77) Protein, amino acid, and glucose deprivation can have a direct effect on the developing brain. (78) Studies conducted in Guatemala among a low socio-economic class of rural American women have revealed that supplemental protein and energy intake during pregnancy are normally associated with increased birth weights and mortality among newborn. (79)

A period in the brain development is also known as the “Growth spurt period” which is normally associated with a rapidly increasing metabolic activity and appearance of new functions. In CNS epigenesis, modification of hormone levels and cellular environment appear to be some important factors for the above phenomenon.

Dobbing and Sands have further studied the human embryonic brain and concluded that apart from the brain, the rest part of the bodies have a fall in the total water content from about 92% at 20-22 gestational weeks to 77% in the adult stage. (80) There is a simultaneous rise in the percentage of lipids in the form of myelin and as well as cholesterol in the brain till the age of 4 years followed by a gradual rise up to adult levels. Further, they found that there are two phases of rapid cell multiplication in the brain, one lasted from 10 to 18 weeks gestation and the other in the latter half of the pregnancy. During the initial spike in rapid cell multiplication of the brain, neuroblasts differentiate into neurons along with glial cell multiplication. The latter half is more of the glial cell hyperplasia. (81) Also during these two stages of rapid multiplication of the brain cells, there is a rapid formation of the dendrites too, therefore, resulting in the overall change in the brain weight which is referred to as Brain growth spurt. (82) This brain spurt or growth continues till the second postnatal year. The weight of the whole brain up to the medulla oblongata is about 13.96% to

14>5% of the total body weight from 9 to 28 weeks of gestation. During the course of gestational development, there is a progressive decrease in the DNA content per gram of the nervous tissues from 9 to 28 weeks and in the cerebrum and midbrain the rate of decrease is more or less same up to the 24th week but the rate of decrease slows down to 10% in about 24 to 28 weeks. The rate of DNA as measured by researchers, showed a 30 fold increase in the number of cells from 9 to 28 weeks of gestation in the cerebrum, 15 fold in the cerebellum and about 8 fold in the midbrain. Also, researchers have shown that there was a decrease in the RNA per mg of tissue in 9-24 weeks in the cerebellum and midbrain than in the cerebrum. Also, the same group observed a decrease in the brain protein content from 13 to 16 weeks of gestation with further declination up to the 24th week. Also through C14-leucine studies, it was revealed that the mitochondrial protein content of the human brain was the highest in cerebrum followed by midbrain at early periods of gestation. This level of protein content in the midbrain further increases with increase in the gestational period of the fetus. Nucleic acid concentration was also found to be highest in the earlier period of gestation between the 13 and 16th week of gestation when compared to later periods. Normally no glutamate synthetase activity is detected in the brain but the activity of Gamma-glutamyl transferase in the brain was found to show the threefold increase in its expression in the second trimester and beyond when compared to early second-trimester phase. Therefore Glutamate synthesis is not a prominent feature of the human fetal organs. As the fetus is constantly supplied with the maternal glucose through the maternal circulation, therefore the alternate metabolic fuel also known as the glutamic acid oxidation is perhaps not required. Also, a high level of glutaminase activity was noted in the midbrain and cerebrum during the 9-12 weeks of gestation which is absent in the initial weeks of brain development. Further another important point that was observed by researchers that from 7th to 28th week of gestation, the total weight of the brain forms almost a constant percent of the body weight.

Fetal CNS development up to 2nd trimester:

The CNS is developed from the neuroectoderm characterized by its immobilization. The earliest neural activity originates from the spinal motor neurons. (83) The early fetal period marks the beginning of the supraspinal control on motor activity and by 9th week the brain stem, the diencephalon, and cerebral hemispheres are formed. (84, 85) Facial nerves controlled by the V and VV cranial nerves start to appear around 10-11 weeks of gestation. After the 12th week, the fetal can start the movement and become variable in speed and amplitude. (86) Late of mid of the second trimester controls the eye movement. (87) The second trimester also marks the beginning of the increase in the complexity of movements and patterns. (88) Development of the pain receptors and when the fetus feels pain is something that is still enigmatic and unknown to researchers. It is believed that functional thalamocortical connections which are required for increased awareness develop between 22 and 26 weeks and beyond thereby giving an idea that the fetus probably starts to fell and perceive pain stimuli during this period.

Genetic and Epigenetic perspectives of fetal Development up to 2nd semester:

DNA methylation and histone modifications both involve chromatin remodeling and contribute towards fetal metabolic reprogramming and the failure of such reprogramming leads to coronary heart disease, Type 2 diabetic disease, and retarded intrauterine growth. David Baker and his co-workers further in 1943, found a correlation between adults having high blood pressure having small babies with large placentas. According to them, fetuses having an impaired supply of nutrition try to adapt to their surroundings by changing their physiology, metabolism, and sensitivity of tissues leading to an abnormal growth and development in a later period. This is now known as the “Thrifty phenotype hypothesis”. Therefore there is a dynamic cross-talk between the mother and the fetus including the strict regulation of gene expression and other epigenetic modifications such as DNA methylation, covalent post-translational histone modifications which mediate phenomena such as

genomic imprinting, chromatin remodeling and eventually an explanation for the molecular expansion of fetal metabolic reprogramming. (89)

Molecular and structural development of the human fetal liver:
Expression of albumin, trans-therein and alpha-fetoprotein (AFP) in the ventral endodermal region marks the first molecular evidence of liver development. Wnt signaling pathway has also an important role in the liver development as its anterior repression helps in maintaining the foregut identity during the primitive gut patterning. This allows the subsequent liver development and is achieved by inhibitors of Wnt signaling pathway by the endoderm. (90)Liver bud formation initiates from the formation of the primitive gut in 22 days in human fetal development. The liver diverticulum is lined by endodermal cells and is called the hepatoblasts which become columnar and undergo a transition into a pseudostratified epithelial layer. (91)

These hepatocytes proliferate and form an s tissue bud delineated by an ECM/basement containing ECM proteins such as laminin, fibronectin, collagen IV and heparin sulfate proteoglycan. During the fetal hepatic development, a number of transcription factors control its onset, which is actually evident from knockout studies in mice models. These models have shown that homeobox factor or He's gene helps in the promotion of hepatoblast proliferation and kinetic nuclear migration. GATA-6 was also required to maintain the differentiation state of the hepatoblasts.(91) Other factors like overexpression of E-Cadherin are important as they help in the better cell to cell connection which is an essential and integral part of a complex tissue architecture development and formation in the fetal stages. Late stage migration of the hepatoblasts to ectopic sites is prevented by the secretion of inhibitory factors which blocks the activities of Matrix metalloproteinases and mesenchymal cells. (92)

Fibroblast growth factor signaling is highly evolutionary conserved and is also essential in case of hepatic development as it is controlled by the activation of the MAPK pathway. Apart from FGF, GATA-6, BMP4 is also highly expressed in the septum transverse mesenchymal cells at an early stage of liver development. Hepatocyte growth factor or HGF is expressed in the septum transversum, the hepatoblasts, and the endothelial cells. A signaling cascade mediated by the SEK1/MKK4 and possibly by c-Jun indicates the hepatoblast differentiation process. (93) TGF-Beta pathways, Smad2/3 also helps in the proliferation and its mutation studies in mice have shown liver hypoplasia. Hepatoma-derived growth factor or HDGF is also produced by fetal hepatoblasts and stimulates in vitro proliferation. This level remains high at the hepatoblast stage and is extinguished when the hepatoblasts mature to hepatocytes. (94) Also, TNF stimulates a signaling cascade which activates the NF-kappa Beta composed of subunits p50 and P65 and its mutation in mice has shown massive apoptosis of the liver cells. Sox9 present in the endodermal cells becomes repressed at the invasion of cells to the septa transverse, however, it reappears at a later stage of development and is restricted only to biliary cells. Therefore it can be concluded that Sox9 is considered to be the earliest indication of biliary cell lineage differentiation. The metabolic and cellular functions of hepatocytes is normally regulated by various transcription factor activators and other related co-factors. The fetal liver remains in contact with two major venous systems namely the umbilical and the vitelline veins. This vitelline vein helps in the formation of the efferent system of the liver. The umbilical vein is the major efferent vessel in the fetal liver and once it disappears or collapses the portal vein replaces it as the major afferent vein. Hepatic artery development occurs after the venous development. Sinusoids are the first blood-forming vessels during pathogenesis, developed by angiogenesis from pre-existing vessels in the septal transverse mesenchyme. With progressive fetal development, the sinusoidal cells gradually adopt the functional and structural characteristics of mature sinusoids. The molecular function of this phenomenon is still not well understood. Wnt2 was shown to be expressed in rat hepatic sinusoidal endothelial cells and could increase their proliferation through activation of canonical Beta-catenin pathway.

Recent studies have shown that mesothelial cells derived from the septum transversum mesenchyme and pre-epicardium can give rise to both stellate and endothelial cells. (91) Although no direct roles of Kuppffer cells have been found in liver organogenesis, these cells might be involved in maturation of erythrocytes during fetal liver hematopoiesis and could be possibly mesenchymal in origin. (95)

After 29 days of fertilization, the enlargement of the gall bladder happens with the presence of a cystic duct at the 34th day. In a 34 day old embryo, the common hepatic duct comes in direct contact with the developing liver. During the 5th week of development, a rapid endodermal proliferation takes place and by 12 weeks of gestation, the distal portion of right and left hepatic duct develops from the extrahepatic ducts and is clearly defined by tubular structures. Intrahepatic bile duct first appears in the 7th week. (96) Around 8th week of development, the primitive hepatoblasts adjacent to the mesenchyme becomes more immunoreactive. Recent research has revealed that biliary cell differentiation is induced in the fetal liver by Activin/TGF Beta and its inhibitors. In about 12 weeks of gestation time, a progressive remodeling of the ductal plates takes place. By 20 weeks of gestation, weak immunoreactivity for cytokeratin appears in the cells of the developing ducts.

Development of the human fetal kidney in the first and second trimester:

The kidney development plays a very important role in keeping the skeleton stronger by keeping the Vitamin D synthesis up-regulated and is also classified as a major organ and the site for the synthesis of Erythropoietin or EPO for effective erythropoiesis during the fetal development. The kidney maintains blood pressure by regulating the Renal Angiotensin System or the RAS. (97)The urinary system also serves the role of maintaining electrolyte and water balance in the body. Nephron development is accompanied by the formation of Pronephrons which are a small group of nephrotomes developing in the cervical region. These are normally short-lived and remain non-functional and are regressed by the 4th week due to the formation of Mesonephrons which develops in the thoracic and lumbar region. By the 5th week, a pair of ureteric buds appears sprouting from the distal mesonephric duct and develops top form the Meta nephron. (97)By early 4th week, 5 to 7 paired of cervical segments of intermediate mesoderm gives rise to a small but hollow ball of epithelium also known as nephric vesicle or nephrectomy or pro nephrons. By day no. 24 and 25, these also disappear. By the start of a 4th week, nephric tubules begin to develop in the form of swellings also termed as mesonephroi or Mesonephric Bridge. About 40 mesonephric tubules develop in craniocaudal succession. By the 5th week, the cranial region of the mesonephros goes into massive regression resulting in the remaining of only 20 pairs of tubules. The appearance of mesonephric ducts occurs at 24 days. (97) A pair of solid longitudinal rods is formed which later on gets transformed into the mesonephric duct. These units function between 6-10 weeks time and gradually gets regressed. The final stage of kidney development is the metanephric stage which starts as early as the 5th week. Ureteric bud mediate which are a pair of the new structure comes out of the intermediate mesoderm at the sacral region from the distal mesonephric duct position in about 28 days. (97)

In the 6th week, the developing metanephros consists of two lobes and acquires 14-16 of them by the end of the 16th week. Urine produced by the mature Nephron flows through collecting tubules, minor calyces, major calyces, the renal pelvis and the ureters finally. By the 6th week, ureteric bud forms 16 branches which coalesce together to form the major calyces extending from the renal pelvis.

By the 7th week, next four generation of branches combine together to form the minor calyces and by the end of 32 weeks, 11 additional branching takes place from 1-3 million branches which form the collecting ducts. The Nephron is formed as a vesicle from the cap of the metanephric blastema. By the 10th week, the Distal Convoluted Tubule unites with the collecting duct to make metanephroi functional. (98)

The kidney gets it complete architecture by the 5-15th week of development when the outer cortex consists of Nephron and the inner medulla with collecting ducts and Loop of Henle. Within the renal pyramids, minor calyx drains a tree of collecting tubules. The renal neurons arise from metanephros in their early development. (99)

Ontogeny of the Human Fetal Immune System:

A pregnancy can be spontaneously aborted in 10-20% of cases without any apparent reason. (100) Ontogeny of a human fetal immune system during its mid-term development is obtained from a set of stem cells. At about 6 weeks of gestation, time, the thymus arises from the third branchial arch and over the next 2-3 weeks, the lymphoid cells migrate from the yolk sac to the liver and from the bone marrow to colonize the fetal thymus. (101, 102) Initial stages of hemopoiesis occur in the yolk sac mesoderm and the extra-embryonic mesenchymal tissues. By 3-4 weeks time of gestation, pluripotent erythroid and granuloma CRO phage progenitors appear in the yolk sac. 5-6 weeks of gestation, primitive cells can be detected in the circulation and from 4 weeks onwards they migrate to the liver which becomes the major site for hemopoiesis. Liver size increases including the number of nucleated cells from 5-10 weeks. Fetal blood collected via fetoscopy at 12-19 weeks of gestation yields both high levels of erythroid and granulocytic/monocytic progenitor cells.(103) Neutrophils appear in the blood during fetal life.(104)The thymus and spleen are seeded from the lover and presence of stem cells in the bone marrow can be detected at 11-12 weeks of gestation. (105)In the 3rd trimester, the hepatic hemopoiesis regresses. Neonatal differs widely from the adult cytokine expression. (106)There is an increase in Interleukin-1 Gamma receptor expression in a case of cord blood mononuclear cells which can help in preventing infections as they produce less IL-10 than adults. (107)Also, there is an enhanced production of IL-6 and decreased IFN-Gamma in the cord blood mononuclear cells. In cases of pregnant mothers infected with malaria, higher levels of the migratory inhibitory factor or MIF is exhibited in the amniotic epithelial and intervillous cells of infected placenta compared t that of uninfected ones. At around 4 weeks of age, two distinct populations of cells are found with a dendritic/macrophagic structure in the yolk sac and mesenchyme and also at 5 weeks of gestation in the pre-hematopoietic liver. The major population of yolk sac macrophage is MHC Class II –ve and a minor population of MHC Class II positive which are seen in the liver at around 7-8 weeks and lymph nodes at around 11-13 weeks of gestation and in the thymus by 16 weeks time. (108)

These are also present in the gastrointestinal tract, skin, hepatic system, and in 17 weeks the number of hepatic sinusoidal macrophages is low but increases to adult levels in the neonatal period.

In 6-7 weeks of gestational time, HLA-DR positive Langerhans cells are detectable in the skin. (109) Dendritic cells in the cord blood are expressed poorly. (110)

T-Cell development:

8-9 weeks of gestation, CD7 positive T-cell precursors from the fetal liver move to the thymus, where 60% are CD2 positive cells and only 4% are cytoplasmic CD3 positive. At 12 weeks of gestation, the delineation of the thymic cortical and medullary regions occurs following which Hassells' Corpuscles appear. (111)

The early prothymocytes are often regarded as triple negative thymocytes as they do not express CD3 or TCR, CD4 or CD8. (112) Double positive cells are formed, when the progenies undergo subsequent division and express both CD8 and CD4. (113, 114) These undergo positive selection by MHC restriction and around 50 million of these cells die each day during this stage of development. (114) 18-24 weeks of gestation time, a high percentage of CD45 RA positive T cells are present in low

amount of B cells, however, the fetal spleen is invaded by an equal amount of B and T cells and monocytes/macrophages. (115)

Thymus T-cells and lymph nodes express activation marker CD69 and by 18 weeks of gestational time, T cells from the spleen have normal levels of CD3,4,8,2 and 11a making the spleen fully immunocompetent with sufficient accessory to ensure T-cell activation. (116)

Mature Alpha Beta T cells can be found in the periphery of the human fetus as early as 10-12 weeks of gestation. (117) The presence of antigen-specific IgE in the human umbilical cord blood mounts an antigen-specific response of neonatal T and B cells. (118) As early as 8 weeks of gestation, pro and pre-B cells can be detected in the fetal liver and omentum. In the omentum pre-B cells decrease during 13-123 weeks and is transitory, It becomes more prominent in the spleen during this period. (119) CD5 positive B cells can be found in 15 weeks of gestation in the human peritoneal and pleural cavity. (120)

Fetal circulation of CD5 positive cells is much higher than adults and declines with gestational age. (121, 122) There are twice as many as pre-B cells in the livers of 7-14 weeks old fetuses although both small and large pre-B cells are also seen in the liver and bone marrow at all times of gestation. (123, 124) At 8 weeks of gestation, liver pre-B cells express themselves and by 10-12 weeks the surface IgM is expressed on B- cells. By 14 weeks, matured B cells outnumber pre-B cells. (125)13 weeks of gestation mark the presence of IgD and CD24 surface markers. IgM positive cells are also detectable in the lymph node from 16-17 weeks and spleen at 16-21 weeks. (116) B cells are abundant in the bone marrow at 16-20 weeks and B cells in the spleen are diffusely distributed at 22 weeks and then form the primary nodules around 24 weeks and later seen in lymph nodes. B cells which are positive for CD20, 21, 22, HLA-DR and IgM, IgD enters the peripheral circulation by 12 weeks of gestation. (126)

At 10 weeks, early IgG and IgM synthesis occurs in the spleen at large amounts and reaches the maximum concentration at 17-18 weeks of gestation. Serum IgG between 5.5 and 22 weeks level slowly increase showing the greatest increase at the 26th week and significant levels at birth. (116)

IgG which crosses the placenta shows an increase from 20 weeks and maximum at 32 weeks if gestation. IgE synthesis starts in the fetal liver and lungs at 11 weeks and 21 weeks at spleen. (116) Cord blood B cells have a higher level of surface IgM and CD79 compared to the adult. Occasionally IgM negative and IgA negative producing cells are observed in the fetal parotid glands between 20-4-weeks, however in cells producing D, G or E isotypes are not seen. (108)Also, in the fetal thymus double positive cells are present and initiation of the expression of CD25 positive Try cells, CD122 GITR, CTLA4 Treg cells occurs. These enter the fetal lymph nodes and spleen where they acquire a primed/memory phenotype. (127)Eosinophil granulopoiesis occurs in the fetal liver at 5 weeks in the hepatic laminae and again after 20 weeks of gestation in the portal areas. (116)

Haemopoiesis development in the fetus in the 1st and 2nd trimester:

During embryogenesis, the site for hemopoiesis are the extra – embryonic yolk sac, fetal liver, preterm bone marrow and developing the placenta. [128] Erythropoiesis is established soon after the implantation of blastocyst with the appearance of primitive erythroid cells in Yolk Sac Blood Island by the 18th day of gestation [129].

Transforming Growth Factor b (TGF-b), Fibroblast Growth Factor (FGF), Bone Morphogenic Protein-4 (BMP-4) are some of the important factors that play an important role in hemopoiesis. The development of the Yolk sac erythroblast occurs in close association with the formation of the first embryonic blood vessel suggesting that the blood and endothelial cells are derived from common hemangioblast precursor source. (130)

After 7 weeks, hemopoietic progenitors are no longer present in the yolk sac. These primitive erythroblasts continue to circulate up to 12 weeks of gestation [131]. From 9th to 24th weeks of gestation the liver serves as a primary source for production of red blood cells. Between 7th and 15th week of gestation, the liver becomes 60 % hemopoietic.

During 17 weeks of gestation, erythropoietin or EPO transcripts appear in fetal kidney and starts to increase after 30 weeks. Erythropoietin is expressed both in fetal liver and postnatal kidney Like primitive erythropoiesis in the yolk sac and is essential for the continued survival of the embryo [132].

At 6 weeks of gestation, Megakaryocytes are present in the liver while Platelets are first evident in the circulation at around 8–9 weeks of gestation. Also, a small numbers of circulating leukocytes are present in the 11th week of gestation. As early as 7 weeks of gestation, Granulopoiesis is present in the liver parenchyma and in some area of connective tissue. In bone marrow hemopoiesis, hemopoietic cells are first seen in an around 10–11 weeks of the embryo, and they remain confined in the diaphyseal region of long bones till 15 weeks of gestation. (130)

However by 12 weeks of gestation myeloid cells predominate. The bone marrow becomes the major site of hemopoiesis after the 24th week of gestation [133, 134]. Lymphopoiesis is present in lymph plexus and the thymus maturation begins at 9 weeks of gestation. At 9 weeks of gestation, B cells with surface IgM are present in liver and circulating lymphocytes. The circulating lymphocytes are detected in the fetal liver by 13 weeks of gestation. (135) Gower 1 Haemoglobin or Hb Gower is the major hemoglobin in embryo less than 5 weeks of gestation. Hb Gower 2 has been found in embryos of gestational age as 4 weeks and is normally absent in embryos older than 13 weeks [136, 137]

Hb F or fetal hemoglobin is the major hemoglobin of the maturing fetus. [138]. Synthesis of Adult Haemoglobin or HbA can be demonstrated in fetuses as young as 9 weeks of gestation [139, 140]. Fetuses of 9–21 weeks of gestation show an increase in the amount of Hb A from 4 to 13 % of the total hemoglobin. The fetal hemoglobin or HbF concentration in the blood decreases after birth by about 3 % per week and less than 2–3 % of total hemoglobin at around 6 months of age. This rate of decrease is directly related to gestational age and is independent of the environmental or oxygen tension which occurs at the time of birth. At 10 weeks, the mean hemoglobin in fetuses gradually increases from 9.0±2.8 g/dl to 16.5±4.0 g/dl at around 39 weeks. On the other hand, there is a decrease in the number of fetal red cells from a mean of 134 ft/cell at 18 weeks to 118 ft/ cell at 30 weeks of gestation.

The total white blood cell count during the middle trimester is between 4 to 4.59×109/l with 80–85% of lymphocyte and 5–10 % neutrophils. The circulating nucleated red cell decreases from a mean of 12 % at 18 weeks to 4 % at 30 weeks and the platelet count remains greater than 15,000/µ ml from 15 weeks gestation to term [141, 142]

Brief outline of Vasculogenesis and cardiac development:
Vasculogenesis is the process by which a completely new vascular system is formed in the early embryo via the formation of endothelial cells and undifferentiated cells. The development of the mature vascular system occurs via a well-coordinated process in the early embryo and any deviation from it can lead to vascular anomalies cause of which is still unknown. (143)

After vasculogenesis, by which early vessels are formed the primitive vascular elements develop buds and help in the sprouting if new branches and this process of developing new branches from existing vascular structure are termed as angiogenesis. The dilation of these vessels into larger ones is known as the process of arteriogenesis. Vasculogenesis is restricted to embryogenesis only. However, angiogenesis and arteriogenesis occur in adult life also. Factors like VEGF, Angipoietin-2,

and Nitric oxide synthetase are important for the development of vascular structures. Hypoxia normally induces angiogenesis.
The embryo contains two endocardial tubes. At 22 to 24 days approximately the fetal heart moves into a more central position. There, a total of 6 paired aortic arches which develop from the corresponding pharyngeal arches in a rostral to caudal direction. Aortic arch 1 & 2 regress in normal adult humans, the 3rd arch becomes the carotid artery and proximal internal carotid arteries respectively. (143)

The left and right aortic arch forms the part of the arch between the left common carotid and left subclavian arteries and the right and fourth aortic arch the proximal right subclavian artery. 5th aortic arch does not develop and the 6th aortic arch connects the left pulmonary artery to the left dorsal aorta thereby forming the ductus arteriosus. With further development, segments are created along the length of the embryo supplied by intersegment branches found throughout the cervical, thoracic and lumbar regions. The lymphatic system develops from regions of the endothelial cells located along the walls of the anterior cardinal veins which express the PRDX1 gene. The first step in the development of lymph is the formation of 6 lymph sacs which generates additional lymph sacs which spread along the course of developing veins. (143) In normal lymphatic developments the right and left side fuse together at the thoracic level with regression of the right thoracic vessel. The left-sided thoracic duct drains into the left internal jugular vein and the right giving rise to the right lymphatic duct. A network of a lymphatic channel is formed from the original lymph vessels and its maturation is orchestrated through the forkhead box protein C2 or FOXC2. (144) Apart from the Vasculogenesis, the cardiovascular system is also the first major system formed during the early part of the embryo development. By the third week, the primordial heart and the vascular system appear. The development f the cardiac system is essential as it is required to meet the embryo's demand supply for nutrition and oxygen as it can no longer get support alone from the diffusion process although the maternal blood supports the embryo by feeding it with oxygen and other nutritional supports and disposing of wastes and carbon dioxide.(19) The cardiovascular system is mainly derived from the splanchnic mesoderm forming the primordium of the heart, paraxial and lateral mesoderm, neural crest cells from the regions of the caudal limits of the third pair of somites, pharyngeal mesoderm. Endocardium formed from the splanchnic mesoderm migrates and localizes between the primitive myocardium and the endoderm below and N-Cadherin plays a major role in linking the catenins. Wnt signaling pathway is an essential hallmark of cardiovascular development and the heart tube. (145)

In the fetal circulatory, the blood carrying oxygen goes to the fetal heart, brain, and the upper extremities while the rest part of the body receives blood with lesser saturated oxygen. Also, the fetal blood pO2 is lower than the maternal pO2 and despite such; the fetus is not exposed to hypoxia due to its adaptive responses and the hemoglobin concentration of the fetal blood which is 50% approximately greater than that of the mother. (146)Also, the capacity of fetal blood to bind with oxygen is more than the adult blood due to the Double Bohr effect. (147)

Respiratory system development up to the 2nd trimester:

Between 6 to 16 weeks of development, the lung remains restricted to the four stages of development. The neuroglandular stage which is between 6 to 16 weeks of development contains only exocrine gland and by the time it reaches the 16th week of gestation, most of the important components of the lungs are already developed except the part where there is involvement of the exchange of gasses. By 22 weeks time, the Type II pneumocytes start secreting pulmonary surfactant and the deficiency of this can lead to Respiratory distress system (RDS) or hyaline membrane disease (HMD). (19)The canalicular system of the lung maturation is the second important process where

during this time period the passage for airway exchange is formed and is often referred to as the lungs tree. The distal part of the lungs matures more than the proximal part and the lumen of the bronchi and terminal bronchioles gets enlarged. Approximately during the 24th to 26th week that is towards the end of the canalicular period respiration can occur via these passages up to the primordial alveolar sacs. The lung tissue also becomes vascularized by this time period. (148)

Gastrointestinal system development:
During the embryonic phase, the primitive gut already gets developed and starts peristaltic activity in the large intestines by 10 weeks time and in the small intestine by 11 weeks. (149) Amniotic fluid swallowing reflects the fetal CNS maturity and contributes towards the growth, development, and maturation of the fetal gastrointestinal system providing around 10-15% of required nitrogen in the normal fetus. Hypoxia, hypotension, and plasma osmolality also induce fetal swallowing. (150) Neuropeptide Y (NPY), Leptin are the main feeding regulatory factors secreted in the human fetuses as early as the 16-18 week of development. (151, 152) Leptin is implicated in the development of the fetal gastrointestinal tract by the presence of functional Leptin receptors or Ob-Rb in the mucosa. (19) By 13 weeks time, the intestine starts to absorb glucose and water.(19) Enzyme activities increase after 14 weeks of gestation and the first appearance of gastric acidity occurs in a 4-month-old fetus. (19)

Development of the Human fetal adrenal cortex up to 2nd trimester:
At about 3 weeks of gestational time, the premature and presumptive fetal adrenal cortex first appears at the root of the dorsal mesentery. All cells at this stage of the adrenal cortex remain the same and there is no differentiation at this stage. According to Keene, Hewer, and Uotila appearance of a rim of presumptive permanent fetal zone develops which separately develops and ultimately forms the definitive cortex together. (153)Whereas, other scientists like Greenwald and Velan states that the same primitive cortex differentiates into the adult and fetal zone. (154, 155)

At about 8 weeks of gestation, the fetal adrenal gland weighs around 1.5 gram and a layer of presumptive capsule forming cells which are 1 or 2 cell thick followed by another layer of the presumptive adult cortex of 7-8 cells thick and a final fetal layer of 40-45 cell thick are formed. Also, other 1-2 vasculogenic cells are formed. A number of places, islands of blood-forming cells without any attempt formation also occur at this stage of development. The adaptogenic layer consists of cells with small and large nuclei whereas the fetal layers have larger cells. At about 9 weeks of gestation, the vasculogenic layer is more prominent, elongated and is 2-3 cells thick whereas the adaptogenic layer increases its thickness to around 13-14 cells.(153) The thickness of the fetal layer also increases. Blood islands become much smaller in number and some are not enclosed in capillaries and a small number of these cells in the blood islands become mature erythrocytes i.e. non-nucleated cells compared to the fetal layer where all the cells become nucleated. During 12 weeks of gestation time, the adaptogenic layer consists of cells smaller than the fetal cortical cells and is very much less vascularized than the fetal layer. The fetal layer consists of blood in between two rows of cells and non-nucleated erythrocytes. Occasionally within the gland, very large cells are also seen and are termed as Titan cells and its length and diameter are about 3 times more than the fetal cortical cells.(153) The adrenal gland weighs around 25.4 grams and is well demarcated with the 3 layers of cells at around 13 weeks of gestation. The fetal cells are big and the spaces in between the cord of the cells are occupied by blood sinusoids. The adaptogenic layers are same as previous and fetal cells are big and towards the center of the fetal cells. (153)

Further at 17 weeks, the weight of the fetal adrenal cortex becomes 135 grams. At places, the connective tissue is more prominent along with cells. Also, transmigration of the adrenal medulla happens and the capsule splits into two layers. An adaptogenic layer is bodily pushed aside by the transmigrating tissues. At places, they go by themselves without the help of medullary tissues. In some layers, the adaptogenic layer consists few titan cells.(153) The fetal layer consists of large

polyhedral cells. The weight of the adrenal cortex is 240 grams at around 19 weeks of gestation. The adaptogenic and fetal layers show the same general characteristics like before. (153)The capsules are permeated by blood vessels and the medulla gets incorporated in the substances of the adrenal gland. The medullary tissue becomes absent and generally forms disorganized array of cells in the central gland surrounded by fetal cortical cells. (153)

Further at 24 weeks of gestation, the weight of the fetal adrenal cortex increases to 635 grams and the capsule consists of a few layers of connective tissue at some areas. Proliferation continues in the autogenic layers and sinusoids starts developing. Attempts at differentiation of this layer into zona glomerulosa and zona fasciculate occur. (153) Fetal cells are still good looking polyhedral cells containing sinusoids in between the chords. The medullary tissue still remains in a disorganized state within the fetal layer of the cortical cells. The fetal adrenal tissue weighs 1010 gram and the capsule consists of fibrous tissue in the midst of a number of vascular channels, arteries, vein, and capillaries. Sinusoids remain filled with blood. (153)

Growth and maturation of the Human Fetal Endocrine system up to 2nd trimester:
Anterior pituitary develops in 4 stages post 4-6 weeks of gestation. (156,157) Stage I also knew as Pituitary placode. Stage II also was known as Rudimentary Rathke's pouch where invagination of the oral ectoderm forms a rudimentary pouch and invagination of the neutral diencephalon form the posterior pituitary part. Also, Rathke's pouch and neural ectoderm of the diencephalon is critical for normal development of the anterior pituitary gland. Stage III or definitive Rathke' pouch deepens and folds on itself and closes to form the definitive Rathke's pouch and the anterior pituitary stalk is formed by the invagination of the posterior part of the presumptive diencephalon.

Stage IV or the adult stage is where the Rathke's pouch is completely separated from the oral cavity and formation of a complicated sensory organ having 5 different cell types occurs under the influence of several signaling and transcription factors. Remnants of the pituitary tissues may persist in the nasopharyngeal midline. FGF-8, BMP-4 is critical for the formation of pouch invagination and critical signaling of neuroectodermal signals for initiating dorsal pituitary morphogenesis. Wnt 5 and 4, BMP4, FGF-8 are present only in the diencephalon. (158, 157, 159) BMP2 and Sonic Hedgehog or Shh helps in a subsequent ventral formation and early cell differentiation requires Rpx (HESX1) and Ptx (PITX0 expression. Formation of Rathke's pouch requires transcription factors like Lhx3, Lhx4, and Isl-1 which are required for progenitor cell survival and proliferation. Ptx1 is expressed in the oral ectoderm and subsequently in all pituitary cell types whereas Ptx2 mutation can cause Reiger's syndrome. Corticotroph cells are morphologically identifiable at 6 weeks time and become immunoreactive ACTH by 7 weeks. Somatotroph cells evident with abundant immunoreactive cytoplasmic growth hormone expressed at 8 weeks. 12 weeks shows differentiated thyrotrophin and gonadotrophs that can express TSH, LH, and FSH. Prolactin or PRL is detected in the early half of gestation and increases progressively from 12-15 weeks. These PRL receptors are abundant in 1st-trimester fetal tissues and are responsible for growth, skeletal and adipose tissue maturation. (160, 161)

The concentration of dopamine, TRH, GnRH and somatostatin is significantly found in the hypothalamus tissues by 10-14 weeks of gestation. Capillaries develop within the proliferating anterior pituitary mesenchymal tissue around Rathke' pouch by 8 weeks of gestation and intact hypothalamic-pituitary portal vessels by 12-17 weeks. The fetal neurohypophysis gets well developed by 10-12 weeks of gestation and contains both Arginine and Vasopressin (AVP) and oxytocin (OT). (162)By 10-12 weeks of gestational time, the pair of well developed adrenal glands is and this further matures with the increase in the gestation period. (159) The progenitor cells derived from the adrenal glands are from the common neuroectodermal stem cells differentiating into neuroendocrine cells expressing hydroxylase and dopamine Beta hydroxylase with respect to transcription factors like PHOX2B, MASH1, PHOX2A, and dHAND. (163, 164) By 10-15 weeks of

gestation, catecholamines present in the chromaffin tissue and the adrenal medulla has the ability to respond to asphyxia. These catecholamines are responsible and crucial for fetal cardiovascular function and its survival as its absence can lead to fetal death in a majority. (165)The main role of catecholamines is to respond to fetal hypoxia. (166)

Development of the thyroid in the first two semesters:
Parafollicular calcitonin-secreting cells or C cells are structured identifiable by 16-17 days of gestation and by 24 days the median anlage develops a thin, flask-like diverticulum extending from the buccal cavity floor to the fourth branchial arch. (167, 168) By 37-50 days, the dissolution and fragmentation of the thyroglossal duct occur. The lower cells of this thyroglossal duct differentiate to form thyroid tissues and thereby forming the pyramidal lobe of the gland. (169) At 51 days of gestation, the thyroid glands after migrating caudally from the pharyngeal floor exhibit its definitive external form and by 7th embryonic week, it reaches its final position below the thyroid cartilage. Tbx1-Fgf8 pathway in the pharyngeal mesoderm plays an important role in early thyroid migration and development. Genes and transcription factors responsible for thyroid gland development include HEX, TTF1, FOXE1, NKX2-5, PAX8. (170, 171, 172) At 29th day of gestation, Thyroglobulin of Tg starts forming in the future follicular cells and iodide and Thyroxine or T4 synthesis are delayed until the 11th week. (173) Radioactive iodine given inadvertently to the mother during this period might not be harmful, however, a later administration can ablate the fetal thyroid. Early growth and development of the thyroid are not dependent on TSH until the 14th week. At the 10th gestational week, the Thyroxine-binding protein or TBG is detectable and it increases with increase in gestational time. Genes encoding Thyroglobulin (Tg), Thyroperoxidase (TPO) and sodium iodide symporter (NIS) are expressed as early as 7th-11th week gestation period. (174)The receptors of the heart, liver, lung can be also identified by 13-18 weeks of gestation. (175) T4 is the only source of thyroid hormone via placental transfer as it plays an important role in the fetal neuronal development. (176)
Inferior and superior parathyroid glands are developed from the 3rd and 4th pharyngeal pouches in a coordinated fashion along with the formation of thyroid glands. (175) Genes like Sox3, Gata3, CRKL, TBX1, and GCM2 are also involved in the development of parathyroid glands. (177, 178) CRKL and TBX1 mutations are involved with Di George's Syndrome and GCM2 mutation leads to hypothyroidism. Transplacental ATP-dependent calcium pumps to maintain the calcium transfer to the fetal circulation. The absence of fetal parathyroids can result in a low fetal plasma concentration and a loss of the placental calcium gradient.

Development of the gonads in the initial stages of development:
Two antigens give rise to the gonads- the primordial germ cells of the yolk sac wall and somatic stromal cells which migrate from the mesonephros by 4-5 weeks of gestation. (179, 180)
Primitive gonads consist of a surface epithelium, primitive gonadal cords continuous with the epithelium and a dense cellular mass referred to as gonadal blastema. Failure of primordial cells to migrate normally can result in extragonadal germ cell cancers in men. The fetal testes and ovary cannot be distinctly identified until 6 weeks of gestational time, when the testicular cords made of Sertoli cells, appear under the influence of the Y-Chromosome or SRY by increasing the expression of Sox 9. This Sox9 directs the differentiation of Sertoli cells and differentiates. (181)Later the primitive cords lose their connections with the epithelium and the primitive Sertoli cells and Spermatogonia become visible. Leydig cells begin to form at 8 weeks of gestation and makeup about 50% of the cell mass at 14 weeks. (175) This differentiation proliferation and organization of the gonads occurs under the influence of hCG and later FSH and LH from the pituitary gland. Progressive synthesis of testosterone occurs from 10 weeks onwards and by 20 weeks, there is an induction of the development of the male internal genitalia and conversion of testosterone into 5 Alpha dihydrotestosterone in the urogenital tract leading to the formation of prostate and external genitalia. (182)At 8 weeks of gestation, androgen receptors appear in the mesenchyme of urogenital

structures followed by an appearance of receptors in the epithelium during 9-12 weeks of development. Around 15 weeks of gestation time, male phenotype develops. Transabdominal testicular descent occurs between 10-23 weeks of gestation. Loss of functional mutational of SRY or SOX 9 gene produces XY reversal and its gain leads to XX sex reversal. (175)In females, an absence of SRY causes the gonadal blastema differentiation into the interstitium and medullary cords containing the primitive germ cells or oogonia. By 11-12 weeks time, clusters of dividing oogonia are surrounded by cord cells within the cortex while the medulla, consists of largely connective tissues. (183) Primitive granulose cells appear at 12 weeks of gestation time and primordial follicles at about 18 weeks and the number increases rapidly thereafter although the number of oocytes declines rapidly. (175) After 12 weeks, although ovary does not produce any steroids, interstitial cells become capable of steroid production. (184) Estrogen receptors are characterized in the 16th to 23rd week of a human fetus. Pancreas budding occurs from the gut tube and the presence of Sox 9, HNF 3B are required for early gut formation and pancreas specification while PDX1, HLXB9, and ISL1 plays an important role in pancreas development. The islet of Langerhans is developed by the presence of HES1neurogenin 3 or NGN 3. Neonatal diabetes mellitus is caused by agenesis due to the mutation in the PDX 1 gene. By 4 weeks time, the human fetal pancreas can be identified and by 8 to 9 weeks time, Alpha and Beta cells can be identified. Also between 8 to 10 weeks of gestation, Insulin, glucagon, somatostatin and pancreatic polypeptides are measurable. (185) Alpha cells outnumber the Beta cells in the initial phase and reach a peak at mid-gestational stage whereas, at the later part of the fetal pancreatic development, Beta cells outnumber the Alpha cells to an extremely limited way. Therefore, the secretion of Insulin at the fetal blood remains low. Hyperplasia and hypertrophy and hyperglycemia exposure lack deficiency of GH-IGF 1. (186) Pancreatic glucagon content remains high during the mid-gestation period, however, it lacks in the fetus which is due to the presence of relatively stable fetal serum glucose concentration maintained by transplacental maternal glucose transfer.

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External links:

Fetal development week by week: http://www.babycentre.co.uk/pregnancy-week-by-week

Fetal Development: MedlinePlus Medical Encyclopaedia:
https://www.nlm.nih.gov/medlineplus/ency/article/002398.htm

Stages of Pregnancy and Fetal Development:
http://my.clevelandclinic.org/health/diseases_conditions/hic_Am_I_Pregnant/hic-fetal-development-stages-of-growth

Further readings:

http://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/prenatal-care/art-20045302

http://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/fetal-development/art-20046151

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