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Review Article

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The Placenta-A Temporary, Multifunctional Organ Does Wonders for The Embryo

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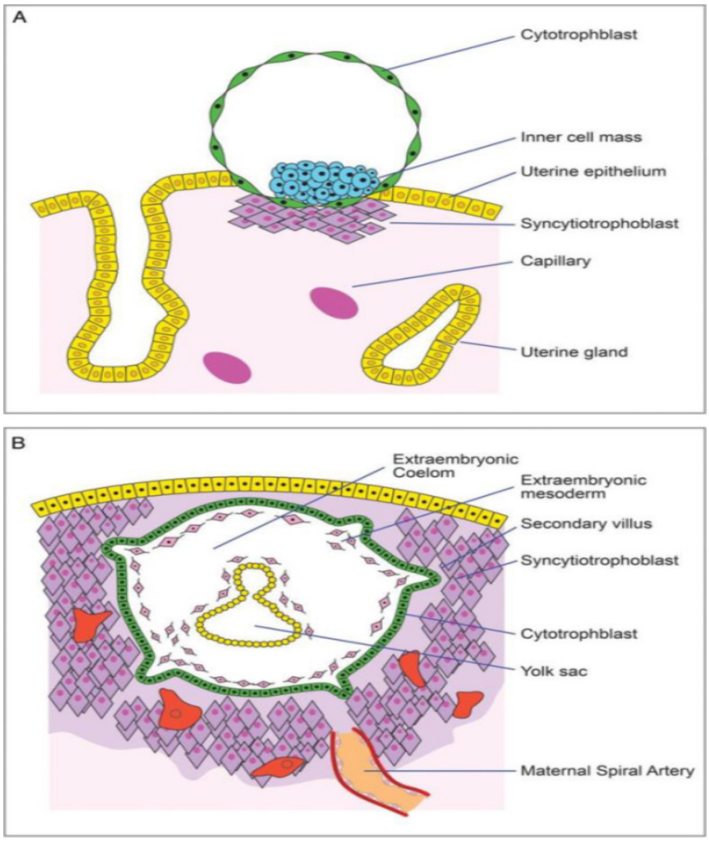
Abstract

Placenta is all in all for the growing foetus; more so it also helps pregnant mothers during pregnancy in many ways, however, the most poorly researched organ. Generally, placentas are discarded after the deliveries but recent findings have shown that even it is useful after deliveries too. Histologically, it has very simple structure, its trophoblast is in a sense unique with response to osmotic shock and thermal stress. Mutation in DNA of mitochondrial trophoblasts can even change the metabolism of newborns. The time line of the placenta is too short (about 40 weeks) but performs and serves as many organs. Recent researches posed unexplainable results for antibody transport. Emerging evidence put placenta as a window to the developing brain.

Placenta is formed when foetus secure a stronghold in the uterine lining. It is derived from the blastocyst at the stage when it contains two distinct differentiated embryonic cell types - the outer trophoblast cells, and the inner cell mass, which is composed of 32 -64 foetal cells [1]. The outer layer of the pre-implantation embryo known as the trophectoderm (TE) and the inner cell mass (ICM) form 5 days post fertilization, and get intimately linked to the maternal circulation for their growth and development. The placenta has 50% cells from the mother and 50% cells from the baby, and can grow up to 1/3 of the baby's weight. Initially, the placenta is in a relatively low-oxygen environment, however, as it grows, it supplies oxygen to the foetus [2].

Placental villi are lined with cells known as cytotrophoblasts and syncytiotrophoblasts with the unique properties described earlier by Paul et al. [3-5]. Trophoblasts are the major focus of Dr. Fisher's research lab, and they discovered that when trophoblasts invade blood vessels, certain proteins on their surfaces called adhesion molecules, are altered to become more motile. One mutation in mitochondrial DNA may be responsible for developing type 2 diabetes in the new-borns. [6]. Trophoblasts change in other ways too by mimicking cells of the blood vessels they invade [7]. Again Fisher et al. examined key aspects of mitochondrial function in placentas from healthy pregnancies and those complicated by gestational diabetes mellitus (GDM) in both whole tissue and isolated mitochondria and observed mitochondrial dysfunction in placental trophoblast cells with mothers experiencing GDM. The spiral arteries, which feed lining of the uterus, become paved with trophoblasts instead of the mother's own cells. Researchers observed the same phenomenon in cancer cells when they metastasize and move away from the primary tumour to invade other parts of the body [8].

The placenta is fully formed by 18 to 20 weeks but continues to grow throughout pregnancy. However, Tracy Bale, has found that not all placentas develop equally; the placenta of a male fetus is more vulnerable to external stress, than the placenta of a female foetus. This vulnerability, in turn, may get transferred to the embryo. Male foetuses are typically larger than females throughout gestation, but they also have higher rates of spontaneous abortions, stillbirth, premature birth and neuro-developmental conditions [9].



Even after delivery the placental tissue contains both foetal and maternal cells: The timeline of placental development shows how the placenta changes over the course of pregnancy. The maximum life span of placenta is about 40 weeks [1]. In this small span of life, it plays a very important role in the welfare of the growing embryo and the mother. It also serves as an immune barrier that protects both the mother and the foetus [10]. The baby's stem cells can travel through the placenta to heal its mother's organs if they are struggling, including the brain, liver, kidney and lung [11]. The placenta also generates cells to protect the mother's heart and fend off breast cancer [12, 13]. In general, cancer during pregnancy is an uncommon occurrence -a survey showed that about 1 in every 1,000 pregnant women is diagnosed with some form of cancer. However, experts expect the number of pregnant women with cancer to increase because more women are waiting until they're older to have children, which increases the risk of developing cancer.

Acts as the Digestive System, Kidney, Lung and Liver

The placenta is a highly complex organ system that functions as the digestive system, lungs, liver and kidneys for the baby: It works as a digestive system by absorbing all necessary nutrients for foetal development and growth [14, 15]. Nutrient and drug transfer across the placenta are by passive and, facilitated diffusion, active transport, pinocytosis, etc.

It functions as the kidneys by filtering out harmful substances, while also letting those that are good for the embryo pass through. No single foetal organ controls foetal fluid volume. True, water flows into the foetus through the placenta since little water is exchanged at any other interface between mother and conceptus [16]. But trans-placental water flow is modulated by the foetal kidneys.

It acts like lungs for the embryo, allowing gas exchange just like the lungs do in a new-born baby or adult [17]. Oxygen and nutrients from the mother's blood are transferred across the placenta to the fetus through the umbilical cord. This enriched blood flows through the umbilical vein toward the baby's liver where it moves through a shunt called the ductus venous.

The placenta does filter out most toxins in the bloodstream before entering the foetus, it cannot act as an impenetrable barrier against all toxic substances [18]. Normally, blood cells and bacteria do not pass through it, but nutrients, water, salt, viruses, hormones, and many other substances, including many drugs, can filter across it. The presence of iodine in table salts is essential for the development of your baby's brain and the nervous system. Iodine deficiency during pregnancy may lead to stillbirths, abnormal brain development, miscarriage, and other medical complications. A semipermeable membrane made up of placental tissues and limiting the kind and amount of material exchanged between mother and foetus shows that thiazides cross the placental barrier and appear in cord blood.

Acts as an endocrine organ

The placenta functions as a major endocrine organ during pregnancy, producing many hormones which affect the status of pregnancy and maternal physiology [17,19]. It also maintains the pregnancy by thickening the cervix, depressing the maternal immune response and preventing ovulation. It also promotes mammary growth.

Steroid hormones: The placenta produces two well known steroid hormones viz. Progesterone and Estrogen. Progesterone maintains pregnancy by supporting the lining of the uterus, which provides the environment for the fetus and the placenta to grow. Progesterone prevents the shedding of this endometrial lining (similar to what occurs at the end of a menstrual cycle), since this would result in loss of the pregnancy. Progesterone also suppresses the ability of the muscular layer of the uterine wall to contract, which is important in preventing premature /preterm labour.

Estrogen levels rise towards the end of pregnancy, which helps in stimulating growth of the uterus to accommodate the growing fetus, and allows the uterus to contract by countering the effect of progesterone. In this way, it prepares the uterus for labour. Estrogen also stimulates the growth and development of the mammary glands during pregnancy, in preparation for breast feeding [20].

Protein hormones: In addition to these, placenta also releases protein hormones, e.g. human chorionic gonadotrophin (hCG), Both men and women have small amounts of hCG in their body at all times because smaller amounts of hCG are also produced in the pituitary gland, the liver, and the colon. However, when a woman is pregnant, her body makes much more hCG than usual [20]. In a healthy pregnancy, the amount of hCG in the blood increases throughout the first 3 months. This hormone is produced primarily by syncytiotrophoblasts during pregnancy, and promotes progesterone production by corpus luteal cells; promotes angiogenesis in uterine vasculature; promotes the fusion of cytotrophoblast cells and differentiation to syncytiotrophoblast cells; causes the block-

age of any immune or macrophage action by mother on foreign invading placental cells [21].

Confirmation of pregnancy: Back in mid 1970s in our laboratory at the All India Institute of Medical Sciences, New Delhi, we developed an anti-beta hCG vaccine (anti-fertility vaccine) using a hCG pregnancy test. Common diagnostic tests are not sensitive enough to detect a pregnancy until hCG has risen to a certain level which means that higher sensitivity test can detect pregnancy earlier. Most women first learn about a pregnancy through a home hCG pregnancy test, and then confirm with blood hCG testing. [13, 22, 23].

Placenta also secretes placental lactogen, placental growth hormone relaxin and kisspeptin. The function of human placental lactogen is not completely understood, although, it is thought to promote the growth of the mammary glands in preparation for lactation. It is also believed to help regulate the mother's metabolism by increasing maternal blood levels of nutrients for use by the foetus. A similar role is played by placental growth hormone, which predominates during pregnancy due to suppression of growth hormone produced by the maternal pituitary gland. Relaxin causes the relaxation of pelvic ligaments and softening of the cervix at the end of pregnancy, which aids the process of labour. Kisspeptin is a recently identified hormone, which is important for many aspects of human fertility. In the placenta, kisspeptin appears to regulate placental growth into the lining of mother's womb (endometrium). A number of other peptide hormones have been recently identified to regulate blood vessel formation within the placenta, which is crucial in allowing exchange of nutrients from the mother to baby; these peptide hormones include soluble endoglin (sEng), soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF) [24].

Fetal protection: Blood Placenta Barrier

Similar to the blood brain barrier (BBB), placenta acts as a blood-placental barrier (BPB) between mother and fetus, but it is the "leakiest" barrier and is a very poor block for chemicals. The placenta is composed of several layers of cells acting as a barrier for the passive diffusion of substances between the maternal and foetal circulatory systems. The passage of a substance across this barrier depends on its molecular size, shape, and charge. Substances not likely to pass through in any significant amount include bacteria, heparin, sIgA, and IgM. Most drugs with MW < 500 Da cross the placenta, and most drugs with MW > 1000 Da do not cross the placenta (ex. heparin, protamine, insulin). Studies in isolated human placenta suggest that efflux transporters are indeed important in limiting drug delivery to the fetus. However, the magnitude of such interactions appears to be modest, and overall less compared to those observed at the blood-brain barrier [25].

Placental abruption results from premature separation of the placenta from the uterus, before the onset of labour. Abnormal formation of the placenta has also been linked with two of the most common pregnancy disorders – pre-eclampsia - which cause a set of symptoms including high blood pressure in the mother, and - fetal growth restriction - where the baby fails to reach its genetically determined growth potential. Both can result in stillbirth and are associated with poor health later in life [26].

During the last 3 months of pregnancy, the baby acquires passive immunity due to antibodies from the mother being passed to her unborn baby through the placenta. Maternal proteins do not traverse the placental barrier, with the exception of immunoglobulins (Ig). Through pinocytosis of syncytiotrophoblast cells the mother transfers to the foetus a variety of Igs she has synthesized during her life [27]. Maternal immunoglobulin G (IgG) is transported across the placenta by an active, neonatal Fc receptor (FcRn) mediated process during pregnancy [28]. This transport can confer short-term passive immunity [1,2,3] and protect infants against infections during their first months of life. Placental transfer of maternal IgG antibodies to the foetus is an important mechanism that provides protection to the infant while his/her humoral response is inefficient. IgG is the only antibody class that crosses the human placenta in significant amounts. Mothers with confirmed COVID-19, SARS-CoV-19 were not detected in the serum or throat swab by RT-PCR in any of their newborns. However, virus-specific antibodies were detected in neonatal blood sera samples. IgG is passively transferred across the placenta from mother to fetus beginning at the end of the second trimester and reaches high levels at the time of birth [29].

Placental Microbiology

Infections involving the placenta may occur, and can be harmful to the foetus if they are passed across the placental barrier. Recent studies have suggested that measuring placental hormones such as sEng, sFlt-1 and PlGF may help to identify women at increased risk of foetal growth restriction and pre-eclampsia.

Maternal infections caused by most organisms which can cross the placenta (including rubella, mumps, poliomyelitis, smallpox, rubeola, syphilis, malaria, toxoplasmosis, and infections caused by S typhosa, V fetus, L monocytogenes, cytomegalovirus, and herpes simplex virus) may result in abortion or stillbirth. Bacteria and viruses of the mother can cross the placenta during the course of pregnancy and actively infect the foetus. However, bacterial infections can be treated effectively in mothers without overt foetal infection.

Two tragic episodes proved that placenta cannot screen out all harmful substances: a rubella outbreak at an Australian military base that resulted in a sudden increase of babies being born blind, and the significant increase of babies born in Germany with deformed limbs because of maternal use of thalidomide. Further, Younge et al. studied the microbiota of human and mouse dyads to understand relationships between microbiota and developing fetus, localize bacteria in the foetus, and demonstrate bacterial viability [30-32]. In human preterm and full-term mother-infant dyads at the time of cesarean delivery, the oral cavity and meconium of newborn infants born as early as 24 weeks of gestation contained a microbiota that was predicted to originate from in utero sources including the placenta.

Gene expression and Disorders of the placenta

Successful placental development is crucial for optimal growth, development, maturation, and survival of the embryo/fetus into adulthood. There is a growing interest in understanding the mechanisms that drive the developmental origins of health and disease, and the role of epigenetic regulation has risen to the forefront of

these studies. In particular, the placenta may be a model organ to consider as a mediator of the impact of the environment on developmental programming of children's health, as this organ plays a critical role in directing development and regulating the foetal environment. Several recent studies have begun to examine how environmental toxicant exposures can impact the placental epigenome, focusing on studies of DNA methylation and micro RNA expression. Numerous epidemiologic and experimental studies demonstrate the profound influence of intrauterine environment on the growing embryo [33].

Functional analysis reveals some patterns of gene expression common to several forms of stress. In situations where sometimes the placenta does not grow properly or attaches low down in the wall of the uterus (a condition called praevia) and in cases where it invades the uterine lining penetrating into the muscle (accreta) are known to have similar gene expression patterns.

The placenta is a wielding force and act as a micro-environmental platform in neurodevelopment as this microenvironment will impair the maternal insults to the process of foetal brain development resulting in the prenatal programming of neurodevelopmental disorder [34].

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