Opinion Article

Barker's Hypothesis and In-Vitro Life

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The British epidemiologist David Barker, perusing the records of births and deaths in 1990, proposed the hypothesis about the influence of intra uterine nutrition on adult onset of diseases (Thrifty phenotype hypothesis).[1] He proposed that poor fetal and early post natal nutrition imposes nutritional thrift on the developing fetus, leading to metabolic diseases like type 2 diabetes mellitus, cardiovascular diseases and hypertension in adult life. In natural conceptions, the embryo and the fetus are exposed only to the in-utero environment and the external factors which can cross the placental barrier. Whereas in assisted conceptions the gametes and embryo are exposed to in-vitro conditions too.

In Vitro Fertilisation (IVF) and Embryo Transfer (ET) has been a major breakthrough in the management of women with irreparable tubal damage[2] and ICSI (Intra Cytoplasmic Sperm Injection) has helped many men with severe semen abnormalities and even azoospermia to achieve fatherhood.[3] These Assisted Reproductive Technologies (ART) are practiced world over and more than 8 million babies have been born.[4] However, the success rates (take home baby rates) still ranges between 30-35% despite innumerable advances in both clinical and embryological aspects of assisted reproduction. Altered hormonal milieu due to ovarian hyper stimulation, in vitro handling of gametes, sperm selection for ICSI overriding the natural selection and culture of embryos with prolonged exposure to culture conditions till blastocyst stage, cryopreservation of gametes and embryos are all very likely to influence the epigenetic make up of the babies, leave alone the endless "adds on" for both the patients and the embryos in culture.

Studies comparing the perinatal outcomes have found increased risk of preterm birth in singleton pregnancies following blastocyst transfer,[5] incidence of autism was higher in ICSI conceived children as compared to conventional IVF[6] and relative risk of having a high birth weight baby was higher in frozen embryo transfer cycles as compared to fresh embryo transfers[7] suggesting increased risk of developing complications in the baby with added interventions.

Follow up studies of the children born out of ART have mostly been limited to the neonatal period,[8] though few cover childhood and adolescence.[9-11] Reproductive history of these children is still sparse and the next generation is yet to be studied in detail. Long term report on health consequences of ART conceived children is not available. Since the first IVF baby is only 41 years old, many diseases of adult onset like diabetes, hypertension, cardiovascular diseases and cancer risk are yet to be observed and reported in these children.

Belva et al[9] studied the reproductive health and puberty of both male and female ICSI conceived children. He found that breast development was less advanced in ICSI females compared to spontaneously conceived children. The median sperm concentration and median total motile concentration was found to be lower in ICSI conceived adolescent males.[10] These observations are still premature and are to be confirmed by large scale studies.

With this anxiety in mind, when reproductive technology explosion is happening in both developed and developing countries with ever increasing interventions, lacking in evidence based conclusions, one wonders “Is it too much, too soon? Is it time to pause and ponder over history, especially about Barker's hypothesis? Does it have relevance in this context?”

Newer methodologies and medical adjuvants are emerging in an urge to improve the IVF success rates. On the other hand this has raised red flags and led to concerns among the medical fraternity with the formation of an international society called Developmental origin of Health and diseases (DOHaD).[12] Efforts are being made to study the influence of novel fertility treatments evolved over the past several decades. In this context Barker's view point about intra uterine influence on adult onset diseases is very much applicable to the present day pell mell in assisted reproduction.

Barker’s hypothesis revolved around “in utero conditions” whereas our concern looms around “in vitro conditions”

Human gametes are single cells with specialized function and structure, meant for in vivo conceptions. It is not surprising that when they are exposed to in vitro conditions in the peri conceptional period, these delicate cells can undergo undetected metabolic, genetic or molecular changes, leaving the progeny to face genetic or imprinting disorders.[13] Newer techniques like time lapse imaging and procedures involving embryo biopsy (preimplantation genetic screening for aneuploidy and preimplantation genetic diagnosis) might have a direct adverse effect on the embryo, while the necessity to extend the culture or cryopreserve the embryos for applying such techniques might further increase the insult on the embryo. When Nature fails to achieve spontaneous conceptions, assisted reproductive technologies are truly rewarding for the desperate couples and physicians. While in vitro work is inevitable, should there be a limit to which we can go to achieve our goal? Are we compromising the health and safety of the next generations to come?

The prime policy of any medical professional should be "primum non nocere". This is even more so for the physicians practising assisted reproduction. We are responsible for the well being of the future generations. It is time to remember David Barker's hypothesis and extend it to the peri conceptional period of assisted reproduction. It is time to revisit the burgeoning innovations in this vital field and to audit them for real application to the needy patients. This is an earnest appeal to all professional societies and regulatory bodies in human reproduction. Pause, ponder and promulgate the needed guidelines.

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