Dear friends,
We have immense pleasure in informing you that we are bringing a journal of our own – ISAR KERALA CHAPTER JOURNAL – from June 2015 onwards. This is a sincere effort to update our knowledge in the field of infertility amongst gynaecologists all over Kerala and we hope that this will increase our awareness to bring recent advances in infertility and share the knowledge. An academic society is said to reach maturity when it launches its own journal in order to share its ideology and good work of its members with the rest of the world. It is a proud moment for all of us as we launch the inaugural issue of the Journal. We congratulate the editorial team for bringing together this issue. This effort will not be possible without your cooperation and guidance which will certainly boost our efforts to make this journal a memorable one.

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Indian Society for Assisted Reproduction, the national body, was established in 1991 under the leadership of Dr. Mahendra Parikh in Bombay. Today, there are 13 State chapters under the national organization. The Kerala Chapter of ISAR was inaugurated on 27th January 2013 at Taj Gateway, Kochi. The office bearers of Kerala Chapter, under the leadership of Dr.K.K.Gopinathan as Chairperson and Dr. T. Fessy Louis as Secretary General, are steering the State Chapter in the right direction.

The state inaugural meeting was hosted along with CME program by CIMAR Hospital and Thiruvanathapuram in January 2014 and the 3rd Annual Conference by ARMC at Kozhikode in January 2015. In the last G.B meeting, it was decided to start a publication of Kerala State Chapter under the editorship of Dr. Sathy. M. Pillai, Vice Chairperson. The journal would include both scientific articles and ISAR news.

In this first issue, there are three articles - Oral Ovulogens, Developmental programming of fetal health, and a case presentation on Congenital Abnormality. Members may use this publication as a platform to share their views, publish scientific articles, connect with fellow doctors and give feedback on the content and style of the journal to the editor for further improvements.

Dr. Ramgopal M Pillai
Sub-Editor ISAR Kerala Chapter Journal

Dr. Sathy M. Pillai
Editor, ISAR Kerala Chapter Journal

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Mild forms of Ovarian Stimulation aims at the development of one or more ovarian follicle to reach the stage of maturity culminating in release of one or more mature oocyte ready for fertilization. Ovaries can be stimulated in two ways; using injectable gonadotropins that directly stimulate ovarian follicular development through gonadotropin receptors or oral agents that manipulate endogenous gonadotropin secretion.

Oral ovulogens fall under two groups; (i) Selective Estrogen Receptor Modulators (SERMS), which have a direct effect on estrogen receptors and (ii)Aromatase inhibitors – which inhibit estrogen synthesis. Clomiphene citrate and Tamoxifen come under SERMS and Letrozole and Anastrozole are the Aromatase inhibitors used for ovulation induction.

Clomiphene Citrate (CC) was introduced in the early 1960’s. It is the most commonly used ovulogen since more than half a century, inspite of the fact that it is a pregnancy risk category X drug. It is stored in the body fat and accumulates in the body at time of implantation, organogenesis and embryogenesis (1-3). Half life is 5 – 21
days, 85% of the drug being eliminated after about 6 days but traces remain in the circulation for more than a month (2).

CC is a non-steroidal triphenyl ethylene derivative and has both estrogen antagonist and rarely agonist properties. It contains two stereo isomers – enclomiphene and zuclomiphene. Of these enclomiphene is the more potent antiestrogenic molecule, mainly responsible for ovulation with a half-life of a few days (1-3). Zuclomiphene is cleared more slowly (>1 month), and accumulates over consecutive treatment cycles (3). CC is cleared through the liver and excreted in the stools.

**Mechanism of Action**

CC binds to estrogen receptors for weeks (unlike natural estrogen), because it has a structural similarity to estrogen. Thus it depletes the estrogen receptor concentration in hypothalamus and pituitary and reduces estrogen negative feedback. This results in gonadotropin releasing hormones (GnRh) production from hypothalamus and gonadotropin (GNT) – LH & FSH from the pituitary. This results in follicular development, estrogen level rises and as a dominant follicle develops the rising estrogen triggers LH surge and ovulation.

The requisites for CC ovarian stimulation are reasonable estrogen levels and an intact HPO axis capable of producing GNT. It is most effective in WHO Type-II anovulation and has no effect in WHO type-I & III groups.

**Dosage (CC)**

50 – 250mg /day x 5 days (Day-2 to Day-6) / (may be extended to 8 – 10 days)

A dose of 12.5mg – 25mg may be used in very sensitive women

Higher the dose – lower success rate

Once ovulation occurs there is no need for further increment. The day of starting CC does not affect the ovulation rate, conception rate or pregnancy outcome in anovulatory women. Pregnancy rate is highest in the first 3 cycles and declines after 6 cycles.

Ovulation occurs in 60 – 80% women, whereas conception occurs only in 30 – 40% women. Cumulative conception after 3 cycles is about 60% and after 5 cycles about 85%. Amenorrhoeic women have better conception than oligomenorrhoeic women.

**Adverse effect of CC**

It is generally a safe drug and well tolerated with minimal side effects.

<table>
<thead>
<tr>
<th>Due to Medication</th>
<th>Due to ovarian stimulation</th>
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</thead>
<tbody>
<tr>
<td>Hot flashes – 10%</td>
<td>Multiple gestation (8%)</td>
</tr>
<tr>
<td>Visual disturbances(&lt;2%) (blurred vision, double vision, scotomata, light sensitivity)</td>
<td>OHSS</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>Ovarian cancer (uncertain)</td>
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<tr>
<td>Pelvic discomfort</td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>Nausea</td>
<td>Pregnancy loss</td>
</tr>
<tr>
<td>PMS type symptoms</td>
<td></td>
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</table>

Most of the side effects are due to the antiestrogenic property of CC, may be dose-dependent and are transient and resolve after the treatment ends. Rarely symptoms persist with severe complications like optic neuropathy, so visual side effects are a contraindication to CC.

CC causes multiple follicular development, thereby increasing the risk of multiple gestation including high order multiple pregnancies. Mild ovarian hyperstimulation syndrome is common, not requiring active management.
Two epidemiological studies (4-5) have shown an association between CC and ovarian cancer. However the risk of ovarian tumors or cancers is still uncertain. There is no evidence that CC increases overall risk of birth defects or any specific malformations. Another paper which has studied the pregnancy outcome in women inadvertently exposed to CC during the first trimester showed no increase in the prevalence of congenital anomalies. Birth weight of babies conceived with CC were significantly lower than those in the control group. The overall incidence of pregnancy loss was slightly higher for clomiphene pregnancies (23.7%) when compared with spontaneous pregnancies (20.4%). Preclinical pregnancy losses were also increased by CC treatment. Spontaneous abortion risk was increased among women, who used CC. However it should be remembered that pregnancy loss in infertile women will be influenced by several other factors such as insulin resistance and genetic factors related to PCOS, endometriosis, unexplained infertility and advancing maternal age.

**Failure of CC**

Failure of treatment occurs in two ways;

(i) Clomiphene resistance – no ovulation in response to CC stimulation

(ii) No pregnancy – patient ovulates but fails to achieve pregnancy

Clomiphene resistance occurs due to either insulin resistance (PCOS) or inappropriate indication as in WHO type-I or III. A third reason for resistance is when the woman has medical disorders requiring treatment such as thyroid dysfunction, hyper-prolactinemia or congenital adrenal hyperplasia.

In women, who fail to ovulate a longer duration of treatment (8-10 days) or higher dose of CC (upto 250 mg/day) may be effective but both these techniques will be associated with more anti-estrogenic effects thereby reducing the chance of achieving pregnancy even if ovulation occurs. Other treatment includes adjuvant therapy with insulin-sensitizing agents (metformin), combination treatment with gonadotropins, dexamethasone, or laparoscopic ovarian drilling.

Failure to achieve a pregnancy may be due to other underlying infertility factors or due to persistent anti-estrogenic effect of CC resulting in discrepancy between ovulation and pregnancy rates. CC also causes an initial rise in LH production from the pituitary in the early follicular phase and this has a negative effect on the ovum and the embryo.

**Anti estrogenic effect of CC**

The anti-estrogenic effects of CC in the periphery (endocervix, endometrium, ovary, ovum and embryo), persist for a very long time due to the long half-life of CC resulting in discrepancy between ovulation and pregnancy rates. Implantation is decreased because of decreased uterine blood flow during early luteal phase and peri implantation stage.

**Management of Anti-E effect**

Administering estrogen concomitantly during CC has been suggested. The results obtained have been controversial with some authors reporting improved pregnancy rates, while others have reported no benefit and a few authors showed even a deleterious effect of estrogen administration. CC may be started earlier in cycle on day-2 instead of day-5 so that the anti-estrogenic effect wears off to some
extent prior to implantation. Tamoxifen, another SERM has more estrogen agonist effect on the endometrium and may be used in place of CC. It has been proposed that high dose soy isoflavones may help to overcome the anti-estrogenic effect of CC on the endometrium.

**Tamoxifen**

Tamoxifen citrate (TMX) is a triphenyl ethylene derivative with a structure similar to CC. Its action comparable to CC but with less anti-estrogenic effect on the endometrium and cervical mucus. Ovulation and pregnancy rates are similar to CC.

**Dosage – 20mg – 60mg /day x 5 days**

It is less frequently used for ovulation induction, although it is sometimes prescribed for women who experience side effects of CC administration, and a meta-analysis has shown comparative rates of ovulation and pregnancy when compared with CC. Tamoxifen may be a better choice in some patients who fail to either ovulate or conceive with clomiphene due to its favorable effect on the cervical mucus and endometrium.

Results regarding effects of fertility drugs on breast cancer risk are conflicting, with some showing no associations and others demonstrating possible risk increases, although different for varying subgroups. In contrast, endometrial cancer results are more consistent, with two recent studies showing increased risks compared to clomiphene usage(6). Some of the endometrial effects associated with tamoxifen therapy in women with a history of breast cancer, are cystic glandular hyperplasia, endometrial polyps and endometrial cancer.

**Aromatase Inhibitor**

Inhibits aromatase enzyme which converts androstenedione to estrone and testosterone to estradiol. Third generation, non-steroidal aromatase inhibitors (Letrozole – 2.5mg tablet; Anastrozole – 1mg tablet) are used for ovulation induction. Letrozole belongs to pregnancy risk category – X and Anastrozole belongs to pregnancy risk category – D.

**Advantages of aromatase inhibitors are that they are:**
- Specific in inhibiting aromatase
- Absence of endometrial receptor depletion
- Oral administration (vaginal / rectal)
- Almost 100% bioavailability after oral admn.
- Short half-life about 45 hours
- No tissue accumulation
- Well tolerated with minimal side effects
- No interaction with other drugs
- Wide margin of safety
- Relatively inexpensive

**Mechanism of Action**

It has a central mechanism and a peripheral mechanism of action. Centrally it blocks estrogen synthesis in the brain and counteracts negative feed back of estrogen on endogenous gonadotropin production. Withdrawal of central estrogen also causes increase in activins, which stimulates synthesis of FSH by a direct action on gonadotropes.

Peripherally it blocks aromatase enzyme and increases intraovarian androgens thereby increasing ovarian follicular sensitivity to FSH stimulation. Increase in testosterone directly augments follicular FSH receptor expression Indirectly
androgen stimulates Insulin like Growth factor-I (IGF-I) which synergizes with FSH to promote folliculogenesis.

**Role of aromatase inhibitor in Ovarian Stimulation**

It promotes monofollicular ovulation and improves treatment outcome when used with GNT. It reduces supraphysiological levels of estrogen thereby reducing the risk of OHSS. It is beneficial in women with estrogen dependent disorders like endometriosis, breast cancer and inherent clotting abnormality. Aromatase inhibitors improve blood flow to endometrium resulting in a positive effect on implantation.

Holzer et al., found that letrozole gave an ovulation rate of 70-84% and a pregnancy rate of 20-27% per cycle in PCOS women resistant to CC. Both Letrozole and Tamoxifen Citrate should be considered as optional therapies for CC-resistant women. In addition, Letrozole was superior to Tamoxifen Citrate in achieving a higher pregnancy and ovulation rate and also lesser side effects in comparison to Tamoxifen.

**Outcome of pregnancies with aromatase inhibitor**

Comparable miscarriage and ectopic pregnancy rates are obtained. There is no increase in the rate of major or minor malformations. There is no increase in the risk of low birth weight as with CC. It is favorable for infertility treatment compared to CC due to short half-life and absence of estrogen receptor antagonism.

**Outcome of pregnancies with clomiphene and aromatase inhibitor**

Rates of miscarriage and ectopic pregnancy with Letrozole were comparable to rates associated with all other pregnancies. A significantly lower multiple gestation rate occurs with AI than with use of CC. CC increases the incidence of small for gestational age infants. No increase in the rates of major malformations in babies conceived after Letrozole treatment has been noted.

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**Fetal Safety of Letrozole and Clomiphene Citrate for Ovulation Induction**

**Insulin Sensitizing Agents**

94 women (Letrozole), 242 women (CC), and 94 (spontaneously.)

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<p>| Table 1. Comparing the effects on pregnancy outcomes of letrozole and clomiphene citrate with controls |
|-----------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>Median maternal age at birth (years) [25%, 75%]</th>
<th>Median birthweight (kg) [25%, 75%]</th>
<th>Median gestational age at birth (weeks) [25%, 75%]</th>
<th>Number of offspring with malformations n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole (94, 78)</td>
<td>33 [30, 37]</td>
<td>3.391 [3.099, 3.808] ( \dagger )</td>
<td>39 [37.6, 40] ( \dagger )</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CC (27', 211)</td>
<td>33 [30, 36]</td>
<td>3.220 [2.540, 3.720]</td>
<td>38.5 [36.7, 40] ( \dagger )</td>
<td>39 [38, 40] ( \dagger )</td>
</tr>
</tbody>
</table>
Letrozole group, 112 babies (14 sets of twins and 2 sets of triplets); CC group, 271 babies (27 sets of twins and 2 sets of triplets); No multiple births in the group who conceived spontaneously. 3.2% babies had congenital malformations in the control group, 2.6% in the CC group had birth defects and Letrozole group had no congenital malformations.

Adjuvant drugs used with ovulogens to improve outcome are insulin sensitizers like Metformin, D-Chiro-inositol, Myo-inositol, N-acetyl cysteine (NAC). Deficiency of Vitamin-D has been found to increase clomiphene resistance and failure of ovulation. Vitamin-D is now known to be an insulin sensitizer and correction of deficiency leads to better outcome.

To summarise, aim of ovulation induction is monofollicular development. Two groups of drugs are used (SERMS & AI). Clomiphene is the most popular drug, but is likely to cause multifollicular development and OHSS. Besides the anti-estrogenic effect of CC reduces pregnancy rate. Letrozole is not licensed for ovulation induction in India. Adverse pregnancy outcome with CC is almost comparable to that following spontaneous conception. Other supporting drugs for ovarian stimulation include insulin sensitizers, Dexamethozone, Bromocriptin, Cabergolin and drugs to correct thyroid dysfunction.

References
Inauguration of ISAR Kerala Chapter by the then National Secretary Dr Rishma Pai, on 27th January 2013 at Taj Gateway, Kochi.

2nd ISAR Kerala State Chapter Conference Inauguration by the Past National President Dr. Dhiraj Gada, on 19th January 2014 at Vivanta by Taj Thiruvananthapuram.

3rd ISAR Kerala State Chapter Conference Inauguration by National President Dr Hrishikesh Pai on 11th January, 2015 at Kadavu Resort, Calicut
Fetal Programming is the idea that the environment in the womb, during different sensitive periods for specific outcome can alter the development of the fetus with a permanent effect on the child. Environmental conditions during development can produce long term changes in the structure and function of cells, tissues and organ systems.

Development is a plastic process, wherein a range of different phenotypes can be expressed from a given genotype. The suboptimal conditions in utero acts upon the developing fetus during the critical and sensitive period of cellular proliferation, differentiation and maturation. This causes structural and functional changes in the cells, tissues and organ system. The response of the fetus to these in utero insults may be in the form of accelerated growth, retarded growth or losing life in utero (Abortion). Evidence suggests that the origins of obesity and metabolic dysfunction can be traced back to the intra-uterine life. These changes have short and long term consequences for health and diseases susceptibility. This is the concept of fetal programming of health and disease risk.

Barker postulated that intrauterine environment will decide how a baby’s metabolism would respond and function for the rest of its life. He found that the lower the birth weight, the higher the risk of dying from heart disease in later life. A lifetime risk for obesity, Type 2 DM, high BP, heart disease, liver and kidney disease are programmed before birth. Barker’s hypothesis has now been proved by many studies all around the world.

Altered nutrition (both under and over) and even maternal stress can alter fetal programming. Any drug or environmental factors at embryogenesis period may affect the development of these organs (Thalidomide). The growth rate of the fetus in the early period due to these environmental influences can have its impact all throughout life extending to the old age.

Prenatal stress of any form – both emotional or physical – in the intra-uterine environment alters the stress biology. From early gestation onwards, placenta produces hormones, neuropeptides, growth factors and cytokines to maintain pregnancy. Placenta protects the pregnancy through immune
tolerance, progesterone and TH1-TH2 balance (T helper-1 & T Helper-2). Cortisol and CRH (corticotrophin releasing hormone) are the critical endocrine mediators for fetal programming in primates. In response to maternal cortisol, the placenta synthesizes and releases CRH in large amounts to the maternal and fetal circulation. The placental CRH concentration is a significant predictor of childhood or adult obesity.

**Fetal programming of adulthood**

The various findings in support of Barker’s hypothesis are as follows:

An intrauterine environment which can adversely affect a baby’s future mostly points towards prenatal stress. Others include undernutrition as well as medications adversely affecting the fetus. Prenatal stress of any form, whether emotional or physical can alter the stress biology. Cortisol and Corticotropin releasing hormone (CRH) are the critical endocrine mediators in the stress biology in the fetus. The prenatal CRH concentration in human pregnancy predicts the rate of fetal growth and size at birth. This in turn is a significant predictor of childhood or adult obesity(1). Another explanation for obesity during childhood is the theory of Brain pull effect in the fetus in response to stress. “The brain pull effect” activates the stress system – both the sympathetic nervous system and the hypothalamic – pituitary – adrenal axis. Increased glucose is allocated to the fetal brain. Sympathetic activity suppresses beta – cell insulin secretion. Insulin independent transport of glucose across blood brain barrier is promoted. The disturbance by the ‘brain pull mechanism’ relates to the onset of obesity in the offspring.

Hurley et al., stated that increased intake of macronutrients during periods of stress and anxiety by pregnant women can cause exaggerated sympathetic tone in the offspring and thereby development of hypertension. Similary increased exposure to glucocorticoids during antenatal period, which again occurs secondary to prenatal stress, can lead to insulin resistance in the offspring(1).

**Stress in infertility**

Infertility and its treatment is a typical example of increased psychosocial stress for ongoing pregnancies. Studies have suggested that many adulthood diseases could be the result of conception mode and interventions done in the embryology lab.

Stress and exposure to abnormal estrogen levels have been associated with growth restrictions and reproductive pathologies including PCOS, altered sexual maturation, Mullerian anomalies, sperm abnormalities and alteration in the histological and molecular endometrial patterns(3).

Psychosocial stress exposure during gestation can exert long term effects on several central and peripheral systems in the offspring. Many adulthood diseases could be influenced by the conception mode and the interventions performed in the embryology laboratory(3).

Epigenetics refers to the mitotically and meiotically heritable changes in gene function that cannot be explained by changes in the DNA sequences. Experimental data from animal studies support the potential effect of ART in changing methylation patterns in gameters and embryos. There is no human studies to support this function. DNA methylation blocks the binding of transcriptional factors at their binding sites. It is reversible form of DNA modification that permits control of many aspects of gene expression. Genes that are not essential for a specific tissue are methylated and thus ‘turned
off' from its expression. DNA methyl transferase enzyme (DNMT 1, 2 & 3) is the methylating enzyme. Loss of methylation induces apoptosis in embryos.

Environmental toxins or dietary modification can have profound effect on methylation and increases the risk of developing disease. The changes in DNA methylation pattern is observed in the early stages of embryo development, when the stem cell population expands and spreads into different tissues. Many insults in early gestation such as IUGR have significant effect on the adult.

**ART and Fetal Programming**

The effect of ART on the offsprings of infertile couples remains controversial. ART children are found to have lower birth weight, shorter gestation duration and increased risk of being small for gestational age and increased incidence of perinatal death. Studies on the offspring of infertile woman born by IVF/ICSI or natural conception, show that the apparent cause of bad perinatal outcome is not ART procedure, but the underlying infertility itself.

Human oocytes, the metaphase –I and germinal vesicle retrieved after COH, present a demethylated pattern in the maternal imprinted region and a gain of methylation in the paternal imprinted region. Whether these changes in methylation seen in human oocytes are due to super ovulation process or patient's age or patient’s inherited infertility itself, is not established. But the ART conceived children do not present a higher degree of imprint variability. Imprinting is the process by which certain genes are inherited in an inactivated or transcriptionally silent state. Imprinting affects gene expression by an epigenetic control.

**Intra Uterine Insemination (IUI)**

There are controversial reports about low birth weight following Intra Uterine Insemination. It was concluded that birth weight abnormalities (low birth weight) in IUI may be due to the underlying infertility.

**IVF /ICSI**

IVF /ICSI offsprings showed higher incidence of IUGR in ICSI twins and lower incidence in singleton ICSIs. The use of ICSI may facilitate the transmission of parental imprinting abnormalities presenting poor quality sperms or Leydig cell dysfunction. Animal studies showed that the maturation media in embryo culture can influence levels of oocyte transcription, imprinting pattern and gene expression. In Vitro culture caused defective placentation, IUGR and behavioural alterations in the offspring. But there are no convincing studies in humans.

**Cryo-preservation**

There are limited studies on birth weight data in case of oocyte cryo-preservation. Transfer of frozen embryo or fresh embryos showed no difference in birth weight. Slow freezing showed no change, but after oocyte vitrification, there was low birth weight and higher prematurity rate.

**Reproductive pathologies**

Fetal growth restrictions, early preterm births, gynaecological diseases in adulthood and hormonal imbalances are the problems in ART. The children are prone to develop reproductive problems in later life.

**Ovarian function**

Animal studies showed that the physiological processes of oocyte and follicle apoptosis is delayed in undernourished fetuses. The children had a high BMI and higher abdominal fat at mid childhood and are prone to develop hyper-lipidaemia and Insulin Resistance which influences the time of menarche.

**Intrauterine Insult and Polycystic Ovarian Syndrome (PCOS)**

Many researches have shown that PCOS has its origin in intrauterine development. Animal studies have proved that androgens
in utero can change oocyte genetic expression pattern and cause abnormal ovarian development, follicular persistence and ovulatory luteal defect. Women with PCOS have higher concentration of androgens during mid-pregnancy and this seems to have a trans-generational effect. Hyperinsulinemia and ovarian follicles are present in the daughters of PCOS mothers before the onset of puberty and persist during pubertal development (4).

**Uterine Development**

DES exposure disrupts the development of Mullerian structures, alters the genesis of endometrial glands, disorganizes smooth muscles. Thonez et al showed that the uterine volume of low birth weight girls is 20% smaller than the normal fetuses. Histological features of endometrium also is altered.

**Sperm Abnormalities**

Exposure to smoking or hormone treatments while in utero impairs spermatogenic function and semen parameters. This may be due to direct effect on the germinal epithelium of testes. Small volume testes, decreased testosterone levels, increased FSH levels, cryptorchidism are seen in infancy of children born to low birth weight mothers. These experimental and epidemiologic data available to support this hypothesis are mainly from animal studies. Further research is ongoing in this field to clarify the mechanism underlying fetal programming(3).

Siffert reviewed the current knowledge about genes. 825T allele of the GNâ3 gene is associated with hypertension, development of obesity, Type-II diabetes and end stage renal disease. It is found that the presence of this gene in healthy pregnant woman without any other detectable risk factors of impaired fetal growth is also associated with lower birth weight.

**Conclusion**

Barker hypothesis postulates that the risk of adult health disorders, particularly metabolic syndrome, is influenced by prenatal environmental exposures (ie, developmental programming). Low birth weight, together with infant catch-up growth, is associated with a significant risk of adult obesity and cardiovascular disease, as well as adverse effects on pulmonary, renal, and cerebral function. Exposure to maternal obesity or high birth weight also represents an increased risk for childhood and adult obesity. In addition, fetal exposure to select chemicals (eg, phytoestrogens) or environmental pollutants (eg, tobacco smoke) may affect the predisposition to adult disease. Animal models have confirmed human epidemiologic findings. Epigenetic modifications (ie, control of gene expression without modification of DNA sequence), occur due to exposure of the fetus to intrauterine stress. To conclude prenatal care should incorporate goals of optimizing maternal, fetal, and neonatal health to prevent or reduce adult-onset diseases.

**References**


4. Fetal programming of PCOS by androgen excess – evidence from experimental, clinical and genetic association studies. JCEM 2006; 91(5)
CONGENITAL UTERINE ANOMALIES

True incidence of congenital uterine anomalies is largely unknown, but studies have shown that the occurrence is almost threefold higher in those with a history of recurrent pregnancy loss. In a comparative study of women with or without a history of recurrent pregnancy loss, using 3D USG, Salim et al., found major congenital anomalies in 6.9% of women with recurrent pregnancy loss, compared with 1.7% in low-risk women (1). They are largely associated with first-trimester abortions, mid-trimester losses, preterm births, malpresentations, and poor pregnancy outcome.

Congenital uterine anomalies occur as a result of incomplete elongation, medial migration, fusion, and septal resorption of the Mullerian or paramesonephric ducts, the defect can occur at any time during the developmental process (2).

Classification

The efforts to classify uterine anomalies was first done by Buttrom and Gibbons in 1979 (3). Later on, many modifications happened. Finally, in 1988 American Fertility Society now known as American Society of Reproductive Medicine came up with a classification which was published in fertility sterility in 1988 (4), it is as follows:

CLASS 1: Mullerian agenesis or hypoplasia
CLASS 2: Unicornuate uterus
CLASS 3: Uterus didelphys
CLASS 4: Bicornuate uterus
CLASS 5: Septate uterus
CLASS 6: Arcuate uterus
CLASS 7: Diethyl Stilbesterol (DES) exposure
Each of these are shortly described below.

**Mullerian agenesis:**
Mayer-Rokitansky-Kuster-Hauser syndrome. Absent uterus and cervix. The vagina may be absent or may form a blind pouch.

**Unicornuate uterus:**
Only one of the ducts develop thus only one side of the uterus is seen. This developed side may or may not be accompanied by a rudimentary horn. This horn can be further subdivided into one with or without a cavity. Sometimes this cavity may communicate with the developed side.

**Uterine didelphys:**
Both the ducts develop independently but fail to fuse. As a result there are two uterus, two cervixes, in most of the cases a vaginal septum is also seen.

**Bicornuate uterus:**
The two uterine horns fail to fuse at the fundus. There is a median cleft due to which the uterus has a heart shaped configuration.

**Septate uterus:**
The two Mullerian ducts fuse but the intervening septum fails to resorb. This is the most common uterine anomaly accounting for almost 55% (5).

**Arcuate uterus:**
It is still debated whether this is an anatomic variant or an anomaly. This is characterised by a slight indentation at the level of the fundus.

**DES Exposure:**
Diethyl stilboesteral is a steroid that was earlier used for recurrent pregnancy loss, premature labour etc to improve the pregnancy outcome. Later it was found to cause uterine malformations in female fetuses exposed to DES in utero. The most common malformation caused is ‘T’ shaped uterus.

**CASE SUMMARY:**
48 years old post menopausal lady came to our centre for infertility treatment. She had been married for 28 years. Her obstetric history showed a left tubal ectopic pregnancy for which she underwent laparotomy 26 years back. She also gave history of one spontaneous abortion 25 years back. There was no other medical or surgical illness.

She was offered donor egg IVF. On preliminary evaluation (hysteroscopy and 3D USG) she was found to have a small uterine cavity and left tubal ostia was not visualized. A diagnosis of right unicornuate uterus was suspected.

She underwent 3 cycles of hormone replacement therapy. Embryo transfer was done with 2 embryos. She conceived with a single intrauterine pregnancy. Prophylactic cerclage was done at 16 weeks. At 20 weeks cervical length was found to be 19 mm. She was put on tocolytics, progesterone supplementation and complete bed rest.

Pregnancy continued till 36 weeks. Ultrasound at 36 weeks showed breech with footling presentation. Elective caesarean section was done at 37 weeks. During the caesarean the diagnosis of right unicornuate uterus with left rudimentary horn was confirmed.

**Conclusion**
Unicornuate uterus is associated with poor
pregnancy outcome including cervical incompetence, premature births and malpresentations. Prophylactic cerclage, tocolytics and progesterone supplementation can be really beneficial.

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