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Review Article

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Effects of Drugs Used to Treat Infertility on Periodontium and Periodontal Disease

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Introduction

Infertility has been described medically as the inability of a couple to achieve conception after a year or more of regular unprotected sexual intercourse or the incapacity to carry a pregnancy to a live birth [1]. The CDC statistics show that on an average one in every eight couple suffers from infertility [2]. The World Health Organization also shows a similar estimate of about 8-10% of the world population suffering from infertility problems [3].

The increasing stress, unhealthy lifestyle and increasing average age of couples opting to start a family in the developed and developing countries around the world are some of the major causes of infertility [4]. However, the tremendous advances in medical sciences in the last two decades have greatly increased the statistics of pregnancies among couples suffering from infertility problems. Some of these revolutionary therapies include hormonal therapy, artificial insemination, assisted reproductive technology (ART), In-Vitro fertilization (IVF), surrogacy etc [5].

Pregnancy is one of the most stressful periods in the life of a woman, both physically and psychologically [6]. In patients suffering from infertility there is a lot more stress involved before conception too [7]. Statistics show that of all the cases, 30% cases of infertility are attributed to the female only, 30% to the male only, 30% to both the partners and 10% cases with unknown causes. Of the 30% attributed to the female, about 25% patients have problems associated with ovulation making it one of the most common causes [8]. This includes Poly cystic ovarian disorder (PCOD), Primary ovarian insufficiency (POI) etc. Some other causes include tubal factors, uterine endometriosis, uterine fibroids, pelvic inflammatory disease, peritoneal problems etc [8].

Luckily majority of these conditions can be corrected through medical interventions like hormonal medications, surgery and ART [9]. Thus a significant number of women undergoing infertility treatment are given some forms of drugs to stimulate the ovaries for ovulation as a first line of treatment. These drugs are also known to aid in controlling the timing of ovulation, increasing the chances of successfully retrieving the eggs for ART [10].

Ovulation induction is done using drugs like clomiphine citrate (cc) and gonadotropin such as follicle stimulating hormone (FSH), Human menopausal gonadotropin (HCG) etc. [11]. Hormones are signaling chemicals that are carried to distant organs in the body by the blood stream and have diverse effects on them. The effects of these hormones and hormonal substitutes administered for infertility are not limited simply to the process of ovulation induction. One such important and often overlooked effect is the effect of these drugs on the gingiva and periodontium.

It is well established that the maternal periodontal health has widespread effects on the developing foetus and recent researches have also found a relationship between the expectant mother's periodontal condition and her fertility status [12]. These revelations indicate an intricate relationship between the hormonal infertility drugs and the periodontal /gingival status of the woman that must be explored in more depth [13].

Hormonal Axis

In humans the menstrual cycle lasts approximately for 28 days and is made up of a number of events controlled by hormones. The event of release of a secondary oocyte from the mature graffian follicle in the ovary is known as ovulation and marks the end of the follicular phase. Though there may be substantial variations in the time period of ovulation, 14.6 days is the average time recorded [14].

The hormones that control the menstrual cycle include estrogen and progesterone which are under the control of the pituitary hormones like Follicle stimulating Hormone (FSH) and Leutenizing Hormone (LH).These hormones are themselves under the control of the hypothalamus. This complex mechanism is known as the hypothalamus-pituitary axis of hormonal control [15].

Clomiphine Citrate

Chemically, Clomiphene Citrate is a citrate salt of clomiphene, a selective estrogen receptor modulator (SERM) [17]. Clomiphine Citrate was originally synthesized in 1956, patented in 1959 but it was in 1967 that it was approved for commercial use [16]. It was primarily used for oligomenorrhea, and its effectiveness in treating infertility and anovulation was accidental when it was realized that

patients receiving the treatment had higher incidences of pregnancy [17].

It acts as a triphenylethylenenonsteroidal ovulatory stimulant that has been used for over thirty five years now as a first line treatment for normogonadotropicanovulatory patients. It is also used for many other disorders like PCOD (Poly Cystic Ovarian Disorder) and even male infertility and low sperm counts. It is most effective in patients suffering from infertility due to anovulation or oligoovulation [17]. It has estrogenic as well as anti-estrogenic activities and competes with estrogen to bind at receptor sites in target tissues [17]. This interferes with the estrogen negative feedback which ultimately raises the serum levels of the pituitary gonadotropin hormones FSH (Follicle Stimulating Hormone) and LH (Luteinizing Hormone). These hormones are responsible for stimulating follicle growth and ovulation [18].

The most common adverse effect associated with the use of Clomiphene citrate is reversible ovarian enlargement and multiple ovulations leading to higher incidences of multiple births like twins and triplets. Today more side effects are being investigated which include ovarian hyper stimulation syndrome, vasomotor flushes and periodontal disease progression [19]. Another treatment option is the use of intramuscular or subcutaneous hormonal replacement with FSH and HMG. These are extremely potent chemicals and bypass the hypothalamus-pituitary-gonadal axis to act on the ovary to stimulate the growth of follicle and ultimately induce ovulation [20].

Relationship to Periodontium

Almost all treatment options involve altering the hormonal regulatory system in some manner. Gingival tissue is known to be extremely sensitive to any such hormonal alterations owing to the presence of specialized receptors like ER beta that have the ability to bind sex hormones and steroids to produce a definite reaction [21].

Estrogen and progesterone have specific receptors on both osteoblast like cells and periosteal fibroblast, periodontal ligament fibroblasts; thus exerting a significant influence on the periodontal environment [22].

The periodontal tissue responses to hormonal fluctuations during pregnancy are well established and pregnancy gingivitis, pregnancy epulis are fairly common. Although a number of causes have been stated; the complex interplay between sex hormones and periodontal tissue still intrigues the scientific community. Very few studies have been carried out to understand the interaction of CC and gonadal hormonal supplements used to treat infertility and gingival/periodontal tissue [11].

One of the first reference studies was carried out by Haytac et al. in 2004. Female volunteers undergoing treatment for infertility and with minimum 25 teeth were included in the study. They were divided into 4 study groups based on the duration and drug protocols used. The first group consisted of 18 women using CC alone for 3 menstrual cycles or less, Group 2consistted of 16 women using CC alone for more than 3 cycles, Group 3 consisted of 21 women using a combined protocol of CC and FSH for at least 4 cycles and the last group consisted of 24 women using combined drug protocol of CC and HMG for at least 4 cycles. Finally an age, education and oral habit matched control group was selected [23]. Statistical differences were recorded in all the study groups in comparison to the controls. Increased inflammation was recorded among women undergoing treatment with CC ($P<0.01$), with those being treated with CC+ FSH ($p<0.001$) and CC+HMG ($p<0.001$). Bleeding on probing and gingival crevicular fluid volume was also found significantly higher in the experimental groups.($p<0.001$) The values were also found higher in case of combined treatment protocols and when the treatment was continued for longer time periods. This study concluded that even when the plaque index was similar, the inflammatory burden was much higher in women receiving drugs altering the hormonal balance to induce ovulation and treat infertility [23].

More recently, in 2013, Sanjay Vasudevan et al conducted a randomized clinical trial in which female subjects were divided into 3 groups, 26 women using CC for 3 menstrual cycles, 26 women using CC for more than 3 cycles, 26 women using Letrozole [24]. The various parameters like Plaque Index, Gingival Index and Sulcus Bleeding index were recorded prior to any periodontal treatment and were reassessed 1 month after oral prophylaxis. These results were compared to the values of the control group that was age, oral habits and education matched (Wilcox on matched) [24]. The scores showed that all test groups showed higher plaque levels and inflammation than the control groups($p<0.05$).Although there was a significant reduction in inflammation after oral prophylaxis, all test groups showed persistence of inflammation compared to the control group [24].

The oral micro flora is another important determinant of periodontal health. Some microbes are known to synthesize steroid metabolizing enzymes and hormonal alterations like in case of assisted pregnancy therapies may contribute to providing a nutritional environment for their growth. Some examples include Aggregatibacteractinomycetemcomitans, Porphyromonasgingivalis and Prevotellaintermedia [25]. Although their involvement in cases treated with CC and or gonadotropins have not been explores, these microbes have been inseparably linked to periodontal deterioration and may play a role in the progression of periodontal disease under high systemic levels of sex steroids.

Conclusion

Recently a number of researches have linked female and even male periodontitis to delayed conception and infertility. The periodontal infections of the mother have also been linked to complications like pre-eclampsia, low birth weight babies and early labor. The ultimate goal of all infertility treatments is to achieve healthy pregnancy and baby. Keeping all these factors in mind it is time that periodontal health is given its due importance. Periodontal checkups and treatments to eliminate all periodontal infections prior to starting any type of infertility treatment must become a mandatory protocol. Regular periodontal checkups throughout the treatment and through the pregnancy will help women cope with the inflammatory stress on their periodontal tissue preventing majority of the complications linked to poor periodontal health.

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