

Chapter 8

Summary And Conclusions

8.1 Introduction

Female infertility is a gynecological multi factorial disorder and its prevalence in the reproductive age women has shown an alarming increase during the most recent decades globally including India with western region of our nation showing a high increase in the primary infertility rate (Ganguly *et al.*, 2010; SRS, 2013; Kaneda *et al.*; 2020; United Nations World Fertility prospects, 2008; niti.gov.in.Total fertility rate 2000-2016; Purkayastha *et al.*, 2021). Challenges of infertility can put down a woman feeling discouraged, especially if there is no evident reason for her being infertile. Numerous apparent medical conditions can contribute to infertility, while sometimes the causes of infertility could be due to other underlying medical conditions which may not be obvious and hence difficult to diagnose. Data in literature on the prevalence of infertility in women with chronic endocrine disorders are however scarce and observational studies in this area should clarify this issue. Some of these abnormalities are "subclinical" which are now must be focused. When reproductive considerations are examined, one possible reason could be thyroid dysfunction. Thyroid hormones have a direct effect on all aspects of female reproduction hence disruption in thyroid function can lead to infertility thus its evaluation in treatment of infertility as well as in treating relevant pathologies become important and it is now imperative to look for hitherto undiscovered underlying risk factors that contribute to this problem. The association of clinical hypothyroidism with female infertility has been documented well globally since long but subclinical hypothyroidism on the other hand even though more common, mostly remains unattended due to its asymptomatic nature must be addressed now (Krassas *et al.*, 2000; Poppe *et al.*, 2007; Jefferys *et al.*, 2015).

Subclinical hypothyroidism is an endocrine disorder characterized by the increased thyroid stimulating hormone levels with normal thyroid hormone levels and no apparent symptoms of hypothyroidism. The data on the studies discussing the prevalence and the role of sub clinical hypothyroidism in etiology of female infertility are scarce and almost nil for the Gujarat population. Subclinical hypothyroidism acts as a silent perpetrator of infertility and goes unnoticed owing to asymptomatic condition. The present study aims to find out the involvement of subclinical hypothyroidism and its consequence to female infertility. The study is designed to screen infertile females of Gujarat for the prevalence of infertility as a subsequence of subclinical hypothyroidism and to look for the etiological effect of the most common factors which are autoimmunity, environmental endocrine disruptors as well as genetic factors. However, such a link of subclinical hypothyroidism and infertility is lacking

both for world and Indian populations with no data for western part of the country. The study aims to find out the independent or cumulative involvement of three etiological factors causing subclinical hypothyroidism which are autoimmune thyroid disease, AITD (anti TPO-Antibodies) (Poppe *et al.*, 2007), Endocrine disrupting chemicals-EDCs (Polychlorinated Biphenyls-PCB), (Diamantiet *et al.*, 2009) and single nucleotide polymorphism-SNPs (*PDE8B* polymorphisms), (Arnaud-Lopez *et al.*, 2008). The study hypothesis states that all these three factors either independently or in combination are affecting the thyroid gland homeostasis leading to subclinical hypothyroidism, which in turn results into female infertility possibly due to reproductive hormones imbalance, increased oxidative stress as well as altered lipid profile as a cause and consequence effect. The study also aims to look for correlation of subclinical hypothyroidism and female infertility with alterations in levels of reproductive hormones, oxidative stress and lipid profile, either independent or as a cumulative effect.

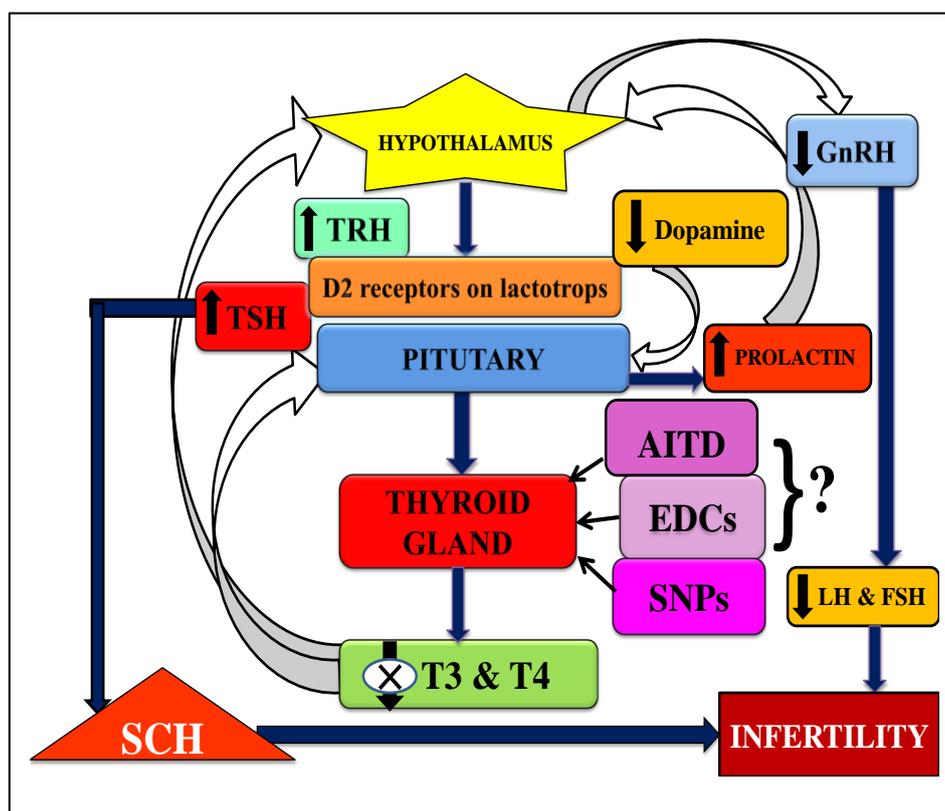


Figure 8.1 Effects of etiological factors on thyroid homeostasis and female reproductive system in Subclinical Hypothyroidism: In subclinical hypothyroidism there is an increase in the TSH levels but the level of thyroid hormones is within the normal range. Etiological factors such as AITD, EDCs and SNPs cause destruction in thyroid gland. Increased TSH causes increased TRH and prolactin levels as a result LH and FSH level decreases resulting into infertility.

8.2 Summary

- Our retrospective population study reports a high prevalence of subclinical hypothyroidism in reproductive age female population of Gujarat with primary infertility and advocating the association (etiology) of thyroid autoimmunity with subclinical hypothyroidism subsequent to female infertility. The study also emphasizes on the concern of female age with increased rate of infertility. The present study also confirms the interference of age, life style, obesity, urbanization and industrialization with subclinical hypothyroidism consequent to primary infertility in reproductive age women.
- Our reproductive hormones estimations in subclinical hypothyroid females with primary infertility report hyperprolactinemia and hypogonadism and high prevalence of menstrual irregularities with oligo-menorrhea and menorrhoea as the common menstrual disorders. Hyperprolactinemia due to subclinical hypothyroidism is also found to be associated with increased age and obesity as well as with hypogonadism and subsequently to primary infertility.
- Our monitoring study for oxidative stress levels and alteration in lipid profile, the study confirms the association of increased oxidative stress levels and altered lipid profile (hyperlipidemia or dislipidemia) with subclinical hypothyroidism subsequent to female infertility.
- Our pilot study reports the association of the exposure, accumulation and toxicity of the environmental endocrine disruptors with thyroid homeostasis precipitating into subclinical hypothyroidism and consequently female fertility for the western part of India.
- Our population study establishes an association of *PDE8B rs4704397* with infertility in subclinical hypothyroid primarily infertile females of Gujarat.

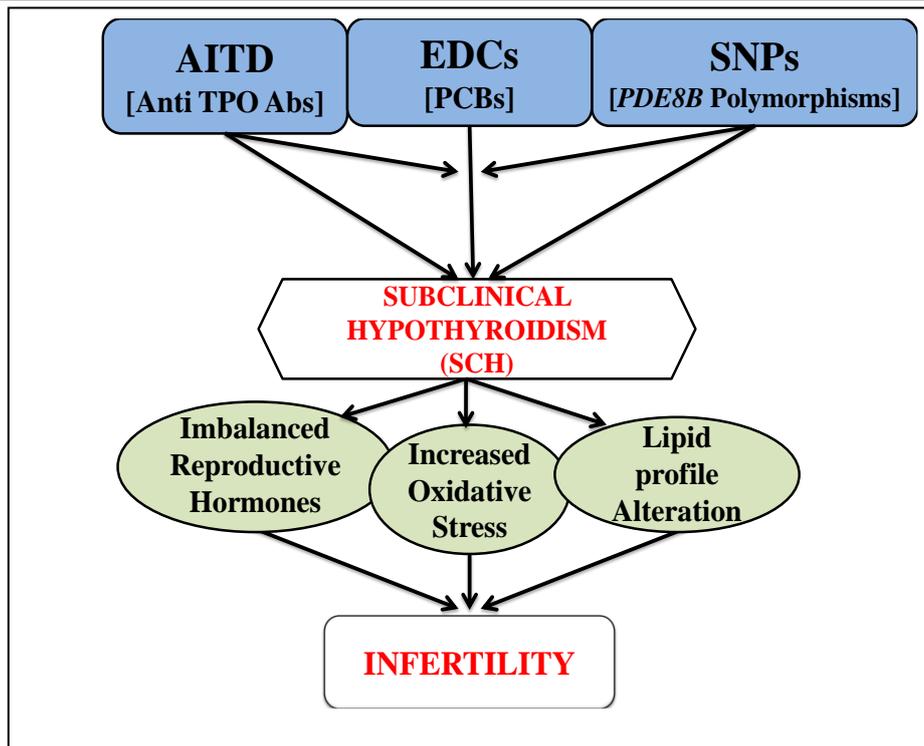


Figure 8.2 Summary: Our population studies show a very high prevalence of Subclinical hypothyroidism in infertile population of Gujarat region. All the three etiological factors,; autoimmune thyroid disease with positive anti-TPO Abs, endocrine disturbing chemical- Polychlorinated Biphenyls and genetic factor-*PDE8B rs4704397* polymorphism chosen for validation of cause and consequence effects were showing the involvement both independently as well as a cumulative effect in causing subclinical hypothyroidism and subsequently infertility in women of reproductive age. Subclinical hypothyroidism further found to be the cause of imbalanced reproductive hormones with increases in prolactin hormone and decreased leutinizing and follicle stimulating hormone levels. Increased oxidative stress levels and altered lipid profile is also found to be associated with subclinical hypothyroidism and infertility in females of Gujarat region. Summarizing autoimmune, environmental endocrine and genetic factor along with the disturbed reproductive hormone levels and increased stress and altered lipid profile can be considered as targets and diagnostic tools for the management and treatment of Subclinical hypothyroidism consequent to female infertility.

8.3 Conclusions

Subclinical hypothyroidism acts as a silent perpetrator of infertility as by and large goes unnoticed owing to asymptomatic condition. Though the potential consequences of subclinical condition can lead to infertility standardized treatment to correct this are uncommon and well-designed clinical trials addressing various unnoticed issues regarding thyroid dysfunction and fertility are still needed. Treating thyroid dysfunction can reverse several abnormalities that impede reproduction and thus improve fertility. Early detection prevents the conversion of subclinical hypothyroidism to overt hypothyroidism by treating with hormones and with careful follow-up. This could then be used to treat infertility with

greater success and less side effects without disturbing the reproductive system. Thus it's a need of an hour that thyroid function test should be routinely recommended for all reproductive age group women, as it helps in detection of hypothyroidism in the early stage, that can be treated medically with hormones and it also cost-effective and unnecessary treatment as well as surgery complications of pregnancy can be prevented and burden to the society is decreased on early diagnosis and management. Early detection prevents the conversion of subclinical hypothyroidism to overt hypothyroidism by treating with hormones with careful follow-up. On the other hand, medications given to alter the levels of reproductive hormones have serious repercussions on the health of females with long-term implications. Treatment of infertility is usually done by direct targeting the reproductive system, instead of looking for the involvement of other factors, such as Subclinical hypothyroidism along with autoimmune, endocrine and genetic factors as cause of infertility. The present study establishes an association of anti- TPO antibodies, polychlorinated biphenyls and *PDE8B* polymorphism with subclinical hypothyroidism in females with infertility hence confirms the etiology of autoimmunity, endocrine disruption and genetic modification in subclinical hypothyroidism subsequent to female infertility in Gujarat population. The present study also advocates the consequences of subclinical hypothyroidism on the imbalance in female reproductive hormones, increase in oxidative stress levels and alteration in lipid profile subsequent to female infertility.

In conclusion, the present study reports a high prevalence of Subclinical hypothyroidism and confirms the association of subclinical condition with female infertility and reiterates the importance of screening subclinical hypothyroidism. The present study further confirms the cumulative etiology of autoimmunity, endocrine disruption and single nucleotide polymorphism in subclinical hypothyroidism. Subclinical hypothyroidism in turn causes an imbalance in the reproductive hormones, increased oxidative stress and alteration in lipid profile subsequent to female infertility, thus the outcomes of the study contributes to our understanding of the etiology of this multi factorial disorder, which can further be used as a diagnostic approach for the management of primary infertility in females.

8.3 References

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