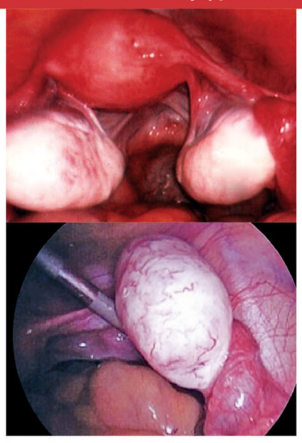
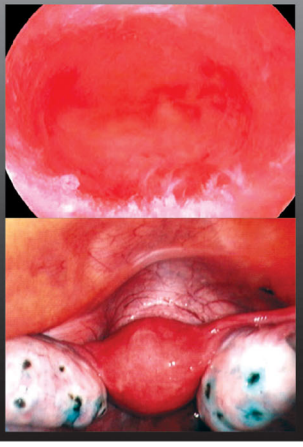
s, visit our website **www.jaypeebrothers.com,** for detailed information on obstetrics & gynecology books, visit our website **www.jaypeebrothers.com**



Practical Management of OVULATION INDUCTION



Editor
Hemant Deshpande

Forewords
PN Razdan
KC Singhal

JAYPEE

Contents

1. Physiology of Ovulation **1**
Shilpa Choudhary, Anjali Deshpande

- Primordial Follicle *2*
- Preantral Follicle *4*
- Antral Follicle *6*
- Autocrine-paracrine Regulation *9*
- Preovulatory Follicle *12*
- Ovulation *13*

2. Endometrium in Ovarian Cycle **18**
Suman Mittal, Anjali Deshpande, Umesh Sabale

- The Endometrium *18*
- Menstruation *19*
- Ovarian Cycle *19*
- Ovulation *21*
- Luteal or Postovulatory Ovarian Phase *21*
- Histopathology of Endometrial Cycle *21*
- Proliferative Phase *22*
- Secretory Phase (Postovulatory Endometrial Phase) *22*
- Hormonal Cycle *24*
- Correlation of Endometrial, Hormonal and Ovarian Cycles *24*
- Imaging the Endometrium *25*
- Fertility and Endometrium *27*
- Potential Functional Markers of Endometrial Receptivity *30*
- Noninvasive Assessment of Endometrial Receptivity *32*
- Role of Hysteroscopy in Evaluation of Endometrium *33*

3. Hypothalamus, Pituitary and Ovulation **38**
Nitin Kshirsagar, A Vivekanand, Bushra Khan

- Oligo-ovulation *38*
- Anovulation *38*

4. Thyroid, Pituitary and Ovulation **46**
Chandrakant Madkar, Nilesh U Balkawade, Priyanka A Dahiya

- Thyroid Disorder and Anovulation *46*
- Anovulation Related to Hyperprolactinemia *48*

Prelims.indd 17 25-07-2015 10:04:18

5. Polycystic Ovarian Syndrome: Past, Present and Future **52**
Pankaj Desai, Jayashree Shridhar, Umesh Sabale

- Polycystic Ovarian Syndrome: The Past *53*
- Polycystic Ovarian Syndrome: The Present *54*
- Etiology *54*
- Diagnosis *58*
- Treatment *64*
- Polycystic Ovarian Syndrome: The Future *67*

6. Ovarian Hyperstimulation Syndrome **70**
Joshi Suyajna, Hemant Deshpande, Rajendra Shitole

- Classification *70*
- Pathophysiology *72*
- Etiology *73*
- Risk Factors *74*
- Epidemiology *75*
- Ovarian Hyperstimulation Syndrome Affects Women of Childbearing Age *75*

7. Ovarian Reserve **84**
Haresh U Doshi, Hemant Deshpande

- Biochemical Tests *85*
- Transvaginal Sonography *85*
- Follicle-stimulating Hormone: Luteinizing Hormone Ratio *86*

8. Premature Ovarian Failure **91**
Atul Munshi, Sujal Munshi

- Possible Causes of Premature Ovarian Failure *92*
- Clinical Features *94*
- Diagnosis *94*
- Importance of Early Diagnosis *95*

9. Ovarian Resistance Syndrome **99**
Veerendrakumar, Priyanka A Dahiya, Umesh Sabale

- Reproductive Aging and Ovarian Insufficiency *99*
- Etiology *100*
- Tests for Ovarian Reserve *101*
- Evaluation of Women *102*
- Long-term Effects *103*

10. Ultrasound in Ovulation Monitoring and Other Diagnostic Tests **105**
Ajit Patil, Umesh Sabale

- Technique of Doing a Transvaginal Ultrasound *105*
- Beginning of Follicular Monitoring *107*
- Pointers Towards OHSS *108*
- Role of Color Doppler *109*
- Secretory Scan *110*

11. Clomiphene Citrate: The Fertility Drug **116**
Habeebullah

- Mechanism of Action *117*
- Indications *118*
- Treatment *119*
- Regimens *120*
- Combination Regimens *120*
- Monitoring *121*
- Contraindications *122*
- Side Effects *122*
- Fetal/Neonatal Anomalies *122*
- Complications *122*
- Male Infertility *123*

12. Gonadotropins in Ovarian Stimulation **126**
Hemant Deshpande, Aritra Pradhan, Surabhi Tomar

- History of Gonadotropins *126*
- Gonadotropin-releasing Hormone Agonists for Ovarian Hyperstimulation *127*
- Protocols *129*
- Controlled Ovarian Hyperstimulation with GnRH Agonists *130*
- Gonadotropin Therapy Monitoring *132*
- Newer Gonadotropin *132*

13. Anastrozole: New Ovulation Drug **135**
Ajith S Nair, Nilesh U Balkawade

- Mechanism of Action *135*

14. Supportive Therapy in Induction **138**
Vidya A Thobbi, Unmesh Santpur, Suguna R Kumar

- Metformin and Ovulation *138*
- Human Chorionic Gonadotropin and Ovulation *140*
- Weight Reduction and Induction of Ovulation *140*
- Myo-inositol *143*

15. Adjuvant Therapy in Ovulation Induction **147**
Unmesh Santpur, Sharankumar Kavalgi

- Dexamethasone (Glucocorticoids) *148*
- Dehydroepiandrosterone *149*
- Chromium *152*

16. Surgical Management of Anovulation **155**
Shreekrishna Kiran, Hemant Deshpande, Vidya Gaikwad

- Technique of Ovarian Drilling *156*
- Mechanism of Ovarian Drilling *156*
- Predictors of Poor Response *157*
- Results of Laparoscopic Ovarian Drilling *158*

17. Oocyte Donation, Ovarian Transplant and Surrogacy **163**
Kanan Yelikar, Shivani Butani, Sharankumar Kavalgi

- Oocyte Donation *163*
- Ovary Transplantation *165*
- Oocyte Donation versus Ovarian Transplant *167*
- Ovarian Tissue Cryopreservation *168*

Index 171

CHAPTER

4

Thyroid, Pituitary and Ovulation

Chandrakant Madkar, Nilesh U Balkawade, Priyanka A Dahiya

JAYPEE BROTHERS

INTRODUCTION

Ovulation is the final process of an orchestrated cascade of signals from hypothalamic pituitary axis to the ovaries. Ovulatory disorder account for 20–30% causes of infertility. In this chapter, we will be discussing anovulation in relation to thyroid disorders and hyperprolactinemia.

THYROID DISORDER AND ANOVULATION

It is common observation and well-known fact that thyroid disorders in women are associated with menstrual disturbances and impaired fertility. The restoration to euthyroid state after treatment shows definite improvement.[1–4] The basic factor which contributes to all these problems is alteration of the physiological concentration of the thyroid hormone either decreased (hypo) or increased (hyper) which has got deteriorating effect on ovarian function.

The relation between thyroid disorder and ovarian function has been well documented in the literature based on *in vivo* studies. Fredrikson and Ryden has noted that thyroidectomy in rabbits arrested maturation of ovarian follicles.[5] Folley demonstrated that thyroid suppressing drugs caused ovarian atrophy.[6] The exact mechanism of the effect of thyroid disorder of the ovarian function is not known but it has been postulated that thyroid hormone might have direct action on ovarian physiology via receptors in granulosa cells. It has also been demonstrated that thyroid has got synergistic action with follicle-stimualating harmone (FSH) causing a stimulatory effect on granulosa cells. Also physiological

Ch 4.indd 46 29-07-2015 15:46:15

concentration of thyroid has got optimal effects on FSH moderated morphological differentiation of the granulosa cells. That is why alteration of the physiological concentration of thyroid hormone has got deteriorating effect on the ovarian function.[7]

Though thyroid hormone plays important role in proliferation and apoptosis of various kinds of cells like muscle cells and lymphocytes, little is known about its action of effect on granulosa cells. A study done by Saiko Asahara, et al. in Obstetrics and Gynecology department of Kobe University, showed that T3 does not affect proliferation of granulosa cells but interacts with FSH to inhibit apoptosis of granulosa cells selectively from small follicles which may interfere with ovulation.[8]

According to Dr John Lowe who is one of the eminent experts in the world about thyroid problems states that 'hypothyroidism' can cause a picture similar to polycystic ovarian disease (PCOD) which has got an important feature of anovulation that might be contributing in thyroid disorder.[9] For the same reason he recommended that before taking a decision of any invasive procedure a trial of replacement of thyroid can resolve cyst and problems of anovulation. A study done by Muderris, et al.[9] has also confirmed the above fact. Some consultants has even considered presence of ovarian cyst as diagnostic marker for hypothyroidism.

Adams WC states that hypothyroidism causes collagen deposition within ovarian intracellular matrix as shown in animal studies. In human, hypothyroidism is characterized by deposition of mucopolysaccharides in the connective tissue of different organs including ovarian stroma and are called myxedematous changes.[10] Also, there is increase in collagen contents ultimately leading to sclerosis as per case report by Hansen, et al. Ultimately all these changes alter paracrine and autocrine mechanism in ovary resulting in disruption of follicular development and altered steroidogenesis.[11]

Ghosh, et al. in their study has concluded that PCOD like feature development is restricted to individuals with subclinical hypothyroidism rather than overt cases. In addition, they have also reported increase in androgen levels in first group more prominent and associated with raised levels of prolactin. It has been claimed that Sex Hormone Binding Globulin (SHBG) levels play a central role in the underlying pathophysiological mechanism of hormonal as well as ovarian morphological changes in hypothyroidism. Low SHBG and concomitant high free T3 levels trigger a vicious circle, which results in ovarian enlargement and cyst formation.[12]

As opposed to increase in size of ovary in hypothyroidism, decrease in size of ovaries was observed in rat models having hyperthyroidism. In addition, it also showed reduction in number of receptors of LH/HCG binding sites per ovary whereas in hypothyroidism the number of receptors is found to be increased.[13]

One important mechanism seen in the patients of hypothyroidism is that there is increase in the level of prolactin due to stimulating effects of thyrotropin releasing hormone (TRH) through the feedback of TSH and thyroid. This increased prolactin level has got effect on ovarian function causing anovulation as discussed in the next chapter.

JAYPEE BROTHERS

Ch 4.indd 47 22-07-2015 15:46:16

In short, there are number of ways by which thyroid dysfunction can modify the ovarian function leading to anovulation. More studies should be done in large group of patients for confirmation of these facts and to search for the newer mechanisms.

ANOVULATION RELATED TO HYPERPROLACTINEMIA

Prolactin is a unique hormone in the female, which is essential for the well-being of mother and baby after delivery. On one side, it causes stimulation of milk secretion[14] essential for baby and on the other side, it provides natural contraceptive protection to mother by inhibition of ovulation and also reduces menstrual blood loss by causing lactational amenorrhea.

Prolactin is polypeptide hormone synthesized and secreted by anterior pituitary gland. This secretion is primarily regulated by the tonic inhibitory response to hypothalamic dopamine.[15] The presence of abnormal high level of prolactin in blood is defined as hyperprolactinemia. Normal levels are 10–28 ng/mL in females and 5–10 ng/mL in males.[16] This is common endocrinopathy frequently encountered in clinical practice.[17]

There is a wide variation in prevalence rate depending upon study population. It is 0.4% in unselected healthy adult population as opposed to 9–17% in women with reproductive disorders. It is also found in 40% cases of PCOD patients. In patients with amenorrhea, it is 9%, galactorrhea 25% and as high as 70% in patients with amenorrhea and galactorrhea.[18,19]

Causes of hyperprolactinemia include: The growth of a prolactin-producing adenoma (40–50% frequency); other tumors of the pituitary region which block the inhibitory influence of the hypothalamus; certain endocrine diseases: primary hypothyroidism (due to the prolactin-stimulating action of thyrotropin-releasing hormone (TRH); polycystic ovarian syndrome (20% frequency); and certain drugs: neuroleptics (phenothiazines, butyrophenones); antidepressants (dibenzazepines); antihypertensives (reserpine, methyldopa); estrogen (high dose).

Clinical presentation of hyperprolactinemia is related to symptoms of hypogonadism. Galactorrhea, menstruation irregularity ranging from oligomenorrhea to amenorrhea and infertility is a triad seen depending upon levels of prolactin, i.e. levels more than 100 ng/mL causes galactorrhea and amenorrhea. About 51–75 ng/mL causes oligomenorrhea and 31–50 ng/mL leads to infertility. The level more than 30 ng/mL is considered to be excessive by clinicians.

Inhibition of ovulation is main factor contributing to infertility which will be discussed. Common causes of hyperprolactinemia are grouped into physiological like pregnancy and lactation period, drug induced (mainly anti-psychotic, antiemetic, antidepressant, antihypertensive and estrogens), HPO axis disturbances like hypothyroidism prolactinoma and PCOD and idiopathic. Among these prolactinoma micro (less than 1 cm) and macro (more than 1 cm)

JAYPEE BROTHERS

is most commonly encountered finding along with other group of idiopathic patients.

Now we will discuss infertility and anovulation in relation to hyperprolactinemia. Hyperprolactinemia inhibits ovulation leading to oligomenorrhea and amenorrhea. High prolactin level directly inhibit the amount of GnRH secretions which results in inhibition of LH and FSH release ultimately leading to anovulation and hypogonadism. Increased prolactin levels also interfers with the positive effect of estrogen on midcycle surge and may directly inhibit steroidogenesis in ovaries. It also interferes with follicle and oocyte development causing atresia of dominant follicle resulting in anovulation. It also hinders normal corpus luteum formation by down regulating LH receptors causing premature destruction of corpus luteum. Thus it has direct action on ovaries causing luteal phase defect and recurrent pregnancy loss.[20]

The estrogen deficient state will also interfere with normal development of endometrium making it unreceptive for implantation. It also inhibits ovarian response to FSH causing less follicular growth leading to hypoestrogenic stage and amenorrhea.

All these factors play their role in postpartum period causing anovulation and lactation amenorrhea.

Hypothyroidism *per se* is a condition which increases prolactin levels by several mechanism. Firstly, there is a compensatory increase in hypothalamic TRH which has got stimulating effect on lactotroph cells resulting in increased secretion of prolactin. Secondly, there is reduction in prolactin elimination from systemic circulation. Finally, primary hypothyroidism can be associated with diffuse pituitary enlargement.[21] So, in hypothyroidism the increased prolactin levels will contribute to inhibition of ovulation. In fact, both these conditions have got synergistic action causing anovulation.

In PCOD patients, the increased prolactin levels are seen in 30-40% patients. PCOD itself causes anovulation and increased prolactin might be having synergistic action in those patients.

Management of hyperprolactinemia—treatment of particular cause responsible for hyperprolactinemia should be done. For example, treatment of hypothyroidism, stoppage or change of responsible drug/treatment of PCOD, etc. We have seen prolactinoma are most common pituitary tumors which can be diagnosed and confirmed by X-ray skull and MRI. Dopamine agonist are the treatment of choice which cause shrinkage of prolactinoma, reduction in prolactin levels and also correct anovulation and amenorrhea. Commonly used drugs are bromocriptine and cabergoline which are considered safe during pregnancy. Regular follow-up is mandatory for such patients till they get cured. In resistant macroadenoma, invasive adenoma and pressure symptoms causing tumors radiotherapy and surgical treatment may be needed. Other dopamine agonist which can be used are pergolide, quinagolide, hydergine but are rarely required.

Bromocriptine can be administered intravaginally. Because absorption is slower, effective blood concentrations persist longer and the drug can therefore

JAYPEE BROTHERS

be given less frequently and at a lower dose (Vermesh, et al. 1988). Long-term treatment with bromocriptine has yielded pregnancy rates of 34–70% in large-scale outcome studies (Tang, et al. 1983; Al-Suleiman, et al. 1989). This compound, however, gives rise to a high incidence of adverse effects (nausea, headache, dizziness) though they are usually mild and transient, and only 5% of patients discontinue the treatment for this reason. Alternative drugs are lisuride, pergolide, quinagolide (Ferrari and Crosignani, 1986) and the most effective recent dopaminergic drug is cabergoline (Webster, et al. 1994; Ferrari, et al. 1995). With cabergoline, a prolactin-lowering drug with long-lasting effect, most patients require doses as low as 0.5–1.0 mg per week. The cumulative proportion of patients in whom prolactin concentrations become normal with weekly cabergoline doses of 1.0 mg or less is 78%. Thus, it may be advisable to use the once-weekly regimen for doses of up to 0.5–1.0 mg weekly, and the twice-weekly regimen for doses over 1.0 mg in order to minimize adverse events related to high single doses.

In patients who do not ovulate even when prolactin concentrations are normal, bromocriptine can be combined with cyclic administration of antiestrogens (Diamant, et al. 1980). If, despite the addition of antiestrogens, ovulation still does not occur, attempts can be made to induce it either using pulsatile GnRH or cyclic administration of gonadotropin. In these patients, restoration of fertility with prolactin-lowering drugs does not increase the incidence of multiple pregnancies or early pregnancy loss, as occurs with gonadotropin therapy (Weil, 1986).

REFERENCES

1. Buxton CL, Herrmann WL. Effect of thyroid therapy on menstrual disorders and sterility. JAMA. 1954;155:1035-9.
2. Gerhard I, Becker T, Eggert Kruse W, Klinga K, Runnebaum B. Thyroid and ovarian function in infertile women. Hum Reprod. 1991;6:338-45.
3. Lincoln SR, Ke RW, Kutteh WH. Screening for hypothyroidism in infertile women. J Reprod Med. 1999;44:455-7.
4. Longcope C. The male and female reproductive system in thyrotoxicosis. In: Bravermann LD, Utiger RD. Werner and Ingbar's The Thyroid, 6th edn. Philadelphia: Lippincott; 1991. pp. 828-35.
5. Fredrikson H, Ryden H. The thyroid-ovarian correlation in the rabbit. Acta Physiol. Scand. 1947;14:136-43.
6. Folley SJ. National Institute for Research in Dairying, University of Reading, Experiments on the relation between the thyroid gland and lactation in the rat. J Physiol. 1938;93:401-12.
7. Maruo T, Hayashi M, Matsuo H, Yamamoto T, Okada H, Mochizuki M. The role of thyroid hormone as a biological amplifier of the actions of follicle-stimulating hormone in the functional differentiation of cultured porcine granulose cells. Endocrinology. 1987;121:1233-41.

JAYPEE BROTHERS

8. Saiko A, Sato A, Aljonaid AA, Maruo T. Thyroid hormone synergizes with follicle stimulating hormone to inhibit apoptosis in procine granulora cells selectively from small follicles. Kobe J Med Sci. 2003;49(5):107-16.
9. Muderris, Boztosun A, Oner G, Bayram F. Effect of thyroid hormone replacement therapy on ovarian volume and androgen hormones in patients with untreated primary hypothyroidism, http://www.ncbi.nih.gov/pubmed/21403408.
10. Adams WC, Leathem JH. Influence of hypothyroidism and chronic gonadotrophin on ovarian collagen in the rat. Endocrinol. 1964;7:138-9. (PubMed).
11. Hansen KA, Tho SP, Hanly M, Moretuzzo RW, McDonough PG. Massive ovarian enlargement in primary hypothyroidism. Fertil Steril. 1997; 67:169-71. (PubMed).
12. Ghosh S, Kabir SN, Pakrashi A, Chatterjee S, Chakravarty B. Subclinical hypothyroidism: A determinant of polycystic ovary syndrome. Horm Res. 1993;39:61-6. (PubMed).
13. Fitko R, Szlezyngier B. Role of thyroid hormone in controlling the concentration of luteinizing hormone/human chorionic gonadotropin receptors in rat ovaries. Eur J Endocrinol. 1994;130:378-80.
14. Jaffe RB, Yuen BH, Keye WR, et al. Physiologic and pathologic profiles of circulating hormone prolactin. Am J Obstet Gynecol. 1973;117:757-73.
15. Pauli S, Kallen C, Wiley ES. Chp no -10 Endocrine disorders and infertility. Gynecology in Practice series—Infertility, Blackwell publication, Sussex, UK; 2011. pp. 90-5.
16. Crosignani PG. Current treatment issues in female hyperprolactinemia. Eur J Obstet Gynecol Reprod Biol. 2006;125:152-64.
17. Barik S, Kundu P. Hyperprolactinemia. In: Mukherjee GG, Chakravarty S, Pal B, et al (Eds). Current Obstetrics and Gynecology. FOGSI; Jaypee Brothers Medical Publishers (P) Ltd, New Delhi; 2007.pp.226-31.
18. Ghumman S. Hyperprolactinemia. In: Step by Step Ovulation Induction, Jaypee Brothers Medical publishers (P) Ltd, New Delhi; 2006.pp.110-27.
19. Josimovich JB, Lavenhar MA, Devanesan MM, et al. Heterogeneous distribution of serum prolactin values in apparently healthy young women, and the effects on oral contraceptive medication. Feril Steril. 1987;47:785-91.
20. Cunha- Filho JS, et al. Hyperprolactinemia and luteal insufficiency in infertile patients with mild and minimal endometriosis. Horm Metab Res. 2001;33(4):216-20.
21. Serri O, Chik CL, Ur E, Ezzat S, et al. Diagnosis and management of hyperprolactinemia. CMAJ. 2003;169:575-81.

JAYPEE BROTHERS

for detailed information on obstetrics & gynecology books, visit our website **www.jaypeebrothers.com,** for detailed information on obstetrics & gy

Practical Management of

OVULATION INDUCTION

Salient Features

- Covers the management of ovulation from all aspects in simple, lucid and user-friendly language
- Deals comprehensively with practical information about ovulation induction
- Focuses on important points in handling cases of anovulation
- Useful for postgraduates and infertility practicing gynecologists.

Hemant Deshpande is currently working as Professor and Head, Department of Obstetrics and Gynecology, Dr DY Patil Medical College and Hospital, Pune, Maharashtra, India. He is a highly experienced person in the field of Obstetrics and Gynecology. He has vast teaching experience and practical knowledge in obstetrics and gynecology. He is also the author of *Textbook of High-Risk Pregnancy*.



Available at all medical bookstores or buy online at www.jaypeebrothers.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers

Shelving Recommendation
OBSTETRICS & GYNECOLOGY

ISBN 978-93-5250-028-4