Infertility Prevention and Management Guideline

Reproductive Maternal and Newborn Health Programme
Department of Public Health
Ministry of Health

2025

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CONTENTS

Acronyms

BHU	Basic Health Unit
ART	Assisted Reproductive Technologies
STI	Sexually Transmitted Infections
PID	Pelvic inflammatory diseases
GnRH	Gonadotropin releasing hormone
FSH	Follicle Stimulating Hormone
LH	Luteinizing Hormone
PRL	Prolactin
CuT	Copper T
HSG	Hysterosalpingogram
HCG	Human chorionic gonadotropin
IVF-ET	In vitro fertilization and embryo transfer
IUI	Intrauterine insemination
ICSI	Intra-cytoplasmic sperm injection
SIS	Saline infusion sonogram
D&C	Dilatation and curettage
USG	Ultrasonography
OCP	Oral contraceptive pills
ATT	Anti-tubercular treatment
DMPA	Depot Medroxy- progesterone Acetate
RTI	Reproductive tract infection

FOREWORD

Infertility is a significant reproductive health challenge, particularly in developing countries like Bhutan. The emotional and psychological burden associated with infertility can be overwhelming, affecting the well-being of individuals and families. However, the advent of assisted reproductive technologies (ART) has brought renewed hope to couples struggling to conceive. Recognizing the declining fertility rate and the importance of offering choices and services for couples facing infertility, the Ministry of Health has prioritized addressing this critical issue.

Our comprehensive approach includes essential diagnostic investigations such as seminal fluid analysis, HSG tubal patency tests, and laparoscopic assessments, along with treatments like ovulation induction and intrauterine insemination (IUI), and introducing advanced techniques such as in vitro fertilization (IVF).

We also recognize that transformative change starts at the grassroot level. Empathetic counseling, acknowledging the concerns and challenges of couples struggling to conceive, and timely referrals can make a significant difference. Preventive measures are equally vital - prompt treatment of reproductive tract infections and immediate care for postpartum or post-abortion sepsis are essential strategies. In addition, adopting a healthy lifestyle, free from harmful habits like smoking and maintaining an optimal body weight, play a key role in preventing infertility.

This guideline is designed to equip healthcare providers across all levels of health facilities to deliver infertility services effectively and in empowering health workers to identify, manage, and seamlessly refer infertile couples to ensure access to advanced care when needed.

Director
Department of Public Health

INTRODUCTION

Infertility is a complex global health issue affecting millions of individuals and couples who struggle to conceive. Around 17.5% of the adult population – roughly 1 in 6 worldwide experience infertility. The prevalence of infertility varies significantly across different regions due to biological, environmental, and socio-economic factors. According to the WHO (2023), the lifetime prevalence was 17.8% in high-income countries and 16.5% in low- and middle-income countries.

Regionally, South Asia is characterized by a high burden of infertility, with an estimated prevalence ranging from 10% to 30%. This disparity is attributed to multiple factors, including infectious diseases, inadequate healthcare services, and cultural practices that affect reproductive health. Within Bhutan, infertility remains a significant yet often overlooked issue. Although comprehensive national data on infertility prevalence in Bhutan is scarce, regional studies and hospital records suggest that infertility affects a notable proportion of couples, requiring urgent attention and intervention.

In Bhutan, the geographic isolation, cultural perceptions, and limited access to advanced reproductive healthcare services compounds the challenges faced by infertile couples. Traditional beliefs and stigma associated with infertility can lead to social isolation, mental health issues, and marital discord. Infertility has significant negative social impacts on the lives of infertile couples and particularly women, who frequently experience violence, divorce, social stigma, emotional stress, depression, anxiety and low self-esteem. Addressing infertility is an important part of realizing the right of individuals and couples to form a family. Furthermore, the lack of specialized fertility clinics and trained healthcare professionals further exacerbates the difficulties in diagnosing and managing infertility effectively.

The National Health Policy (NHP) prioritizes equitable access to sexual and reproductive health services, helping individuals achieve their reproductive goals. To improve infertility services, the Ministry of Health (MoH) has taken significant steps to enhance these services nationwide. Currently, basic services such as counseling and semen analysis are available at various health facilities. Some centers with gynecologists also offer basic ovulation induction. Additionally, the introduction of intrauterine insemination at the national referral hospital represents a progressive move towards more advanced reproductive technologies.

Recognizing the importance of enhancing infertility services, the 13th Five Year Plan (FYP) prioritizes improving access to equitable and high-quality family planning services, including infertility treatments. To streamline and standardize infertility treatment services in Bhutan, this guideline has been developed.

This guideline is a crucial step towards addressing the complex issue of infertility in Bhutan. By adopting a comprehensive, culturally sensitive, and evidence-based approach, the aim is to improve reproductive health outcomes, enhance the quality of life for infertile couples, and contribute to the broader goal of achieving universal access to reproductive healthcare.

Objectives of the Guideline

- To provide a comprehensive framework for the prevention and management of infertility in Bhutan, integrating global best practices with locally relevant strategies
- To guide healthcare providers and policymakers on evidence-based recommendations to enhance reproductive health services across the country

Scope of the Guideline

The scope of this guideline encompasses several critical areas of infertility care:

1. Prevention strategies: Focus on lifestyle modifications and reproductive health education to reduce infertility risk.
2. Diagnosis and assessment: Detailed protocols for evaluating male and female infertility, including diagnostic tests and examinations.
3. Treatment modalities: Overview of medical, surgical, and assisted reproductive technologies.
4. Emotional and psychological support, including counseling services.
5. Ethical and legal considerations: Guidance on ethical standards and legal requirements in infertility treatment.
6. Implementation and monitoring: Mechanisms for program monitoring, evaluation, and professional development of healthcare providers

CHAPTER 1: OVERVIEW OF INFERTILITY

1.1 Definition of Infertility

Infertility in a couple is defined as the inability of couples to achieve conception after one or more years of regular, unprotected intercourse.

When the female partner's age is >35 years old, infertility is defined as a failure to conceive within six months of unprotected intercourse (1). The terms ``subfertility`` and ``Infertility`` are used interchangeably and for this guideline we have adopted infertility.

1.1.1 Types of infertility

1.1.1.1 Primary infertility

Primary infertility is defined as inability to conceive despite unprotected and regular sexual intercourse over a period of 12 months in a woman who had previously never conceived.

Fertility intervention may be started earlier than 12 months depending on medical, sexual, reproductive risk factors and the age more than 35 years. (Table 2)

1.1.1.2 Secondary infertility

When a couple had earlier conceived but subsequently failed to conceive despite unprotected and regular sexual intercourse.

1.1.2 Causes of infertility

Causes of infertility include male factors or female factors. The female factors include ovulatory dysfunction, uterine abnormalities, tubal obstruction, peritoneal factors, or cervical factors. It is found that 40% of the etiological factor for infertility is found in females while 35% were of the male. About 10-20% can be attributed to both and the rest of the causes remain unexplained.

1.1.2.1 Causes of infertility in female

In females, infertility may be caused by abnormalities of the uterus, tubes and ovaries including dysfunctional endocrine system, inflammatory reactions and others.

- **Ovulatory causes**

The most common overall cause of female infertility is the failure to ovulate (anovulation), which occurs in 40% of women with infertility issues.

The World Health Organization has classified anovulation into three main groups, and recognized hyperprolactinemia as an additional cause (Table 1).

Table 1. World Health Organization classification of anovulation

World Health Organization classification of anovulation	
Class 1: Hypogonadotropic hypogonadal anovulation (hypothalamic amenorrhea)	These women have low or low-normal serum follicle-stimulating hormone (FSH) concentrations and low serum estradiol concentrations due to decreased hypothalamic secretion of gonadotropin-releasing hormone (GnRH) or pituitary unresponsiveness to GnRH.eg excessive dieting , weight loss, exercise, stress, and space occupying lesions.
Class 2: Normogonadotropic normoestrogenic anovulation	These women may secrete normal amounts of gonadotropins and estrogens. However, FSH secretion during the follicular phase of the cycle is subnormal. This group includes women with polycystic ovary syndrome (PCOS). Some ovulate occasionally, especially those with oligomenorrhea.
Class 3: Hypergonadotropic hypoestrogenic anovulation	The primary causes are primary ovarian insufficiency (absence of ovarian follicles due to early menopause) and ovarian resistance (follicular form).
Hyperprolactinemic anovulation	These women are anovulatory because hyperprolactinemia inhibits gonadotropin and follicular development; they may have regular anovulatory cycles, but most have oligomenorrhea or amenorrhea. Their serum gonadotropin concentrations are usually normal.

- **Tubal Factors**

  It accounts for 25-35% of infertility and are due to:

  Congenital Defects: There is either absence of tubes or they are too narrow/short

Infections: All infections that cause scarring or blockage of tubes can cause infertility. Infections could be due to N. Gonococci, Mycoplasma, Chlamydia and other gram negative anaerobes, pelvic tuberculosis ; complications of unsafe abortion, postpartum sepsis or abdominal/pelvic surgery.

Other causes: Causes like severe endometriosis, adhesions from pelvic surgeries, appendicitis, and salpingitis isthmica nodosa interfere with tubal transport and blockage

- Uterine Factors account for 5-10% of infertility and are due to:

  Uterine anomalies like septate uterus and bicornuate uterus

  Uterine fibroids with submucosal or intracavitary component

  Intrauterine adhesions are bands of fibrous tissue formed in the endometrial cavity following uterine procedure or infection (Asherman's syndrome).

- **Cervical factors**

  It accounts for 3% of infertility. Congenital malformation and surgery on the cervix or trauma may cause stenosis and inability of the cervix to produce normal mucus which facilitates the transport of sperms, thereby impairing fertility.
- Endometriosis affects 10-15% percent of women of reproductive age. In women with endometriosis, 30 to 50 percent are estimated to be infertile.
- Other factors include autoimmune causes , chromosomal abnormality and luteal phase defects etc

1.1.2.2 Causes of infertility in male

In male, the cause of infertility can be grouped under the following headings:

- **Medical causes:**

  Failure to produce sufficient numbers of spermatozoa: There are lots of conditions which lead to insufficient spermatozoa numbers like
  - Incomplete, late or non descent of testes
  - History of orchitis

- Damage to testes resulting from operation
- Injury or exposure to radiation
- Varicocele
- Tumor
- Tuberculosis
- Syphilis
- Hypogonadism
- Thyrotoxicosis
- Diabetes Mellitus

- **Bilateral obstruction of the epididymis, the vas or the ejaculatory ducts:**
  - Accident or operation
  - Gonorrhea and
  - Tuberculosis; the lesion is usually an epididymitis
  - Congenital absence or gross hypoplasia of the vas

Failure to Deposit Spermatozoa in the Vagina:

- Impotence,
- Hypospadias
- Phimosis
- Retrograde ejaculation
- Drugs which affect ejaculation include, ganglion blockers, the tricyclic antidepressants, MAO inhibitors, phenothiazines, 6-blockers and thiazides

- **Environmental causes:**
  - **Industrial Chemicals**

    Exposure to industrial chemicals, such as pesticides, solvents, and phthalates, adversely affects male fertility by reducing sperm count, motility, and quality. These chemicals can cause hormonal imbalances, oxidative stress, and DNA damage in sperm.

- **Heavy Metal Exposure**

  Heavy metal exposure, such as to lead, mercury, and cadmium, negatively impacts male fertility by reducing sperm count, motility, and viability. These metals can cause oxidative stress and DNA damage in sperm, disrupting hormone balance and impairing reproductive function.

- **Radiation or X-rays**

  Radiation or X-rays can adversely affect male fertility by damaging sperm DNA, reducing sperm count, and impairing sperm motility. High doses can harm the testes and disrupt hormone production, leading to long-term fertility issues.

- **Overheating the Testicles**

  The testicles require a cooler temperature than the rest of the body for optimal sperm production. Prolonged exposure to high temperatures, such as from frequent use of hot tubs, saunas, or tight clothing, can impair spermatogenesis. Overheating can reduce sperm count and motility, potentially leading to infertility. Maintaining an appropriate scrotal temperature is crucial for male reproductive health.

- **Understanding and mitigating these environmental risks is essential for preventing long-term health problems and ensuring overall well-being.**

- **Lifestyle and other causes:**
  - **Drug Use**

    Drug use, including anabolic steroids, opioids, and recreational substances, negatively impacts male fertility by reducing sperm count and motility, causing hormonal imbalances, and leading to abnormal sperm morphology.

- **Alcohol Use**

  Alcohol use adversely affects male fertility by reducing testosterone levels, decreasing sperm count, motility, and viability, and causing DNA fragmentation in sperm. Excessive drinking can also disrupt hormone balance and impair testicular function, significantly lowering the chances of conception and affecting overall reproductive health

- **Tobacco Smoking**

  Smoking tobacco negatively impacts male fertility by reducing sperm count, motility, and overall quality. It leads to DNA damage in sperm, increases oxidative stress, and alters hormone levels. These effects collectively decrease the chances of successful conception, highlighting the importance of quitting smoking for better reproductive health.

- **Weight**

  Weight significantly impacts male fertility. Obesity can lead to hormonal imbalances, reducing testosterone levels and increasing estrogen levels, which negatively affects sperm production and quality. Excess body fat can also cause oxidative stress, leading to DNA damage in sperm. Additionally, obesity is associated with conditions such as diabetes and sleep apnea, which further impair reproductive health. Conversely, being underweight can also disrupt hormone levels and reduce sperm quality and count.

- **Stress**

  The mechanism by which stress affects the quality of semen is not fully understood yet. According to researchers, stress may cause the release of steroid hormones such as glucocorticoids, which can decrease testosterone levels as well as sperm production. Oxidative stress is another possibility and has been found to adversely impact semen and sperm quality and fertility

- **Nutrition**

  There is increasing evidence of the role of micronutrients in fertility. Deficiency of zinc and folate are implicated in decreased spermatogenesis possibly through defective DNA and RNA synthesis. Deficiency of dietary antioxidant micronutrients, e.g. beta-carotene, lycopene, retinol and α-tocopherol may decrease genital tract secretions in men, leading to infertility especially through immunological mechanisms.

- **Adopting healthy lifestyle choices is essential for preventing diseases, enhancing longevity, and improving quality of life.**

1.1.2.3 Unexplained infertility

Infertility in couples with apparently normal ovarian function, fallopian tubes, uterus, cervix and pelvis, age ≤ 40 years and with adequate coital frequency; and apparently normal testicular function, genito-urinary anatomy and a normal ejaculate. (ESHRE guideline 2023)

Approximately 15% of infertile couples are considered to experience “unexplained infertility” (UI) (Guideline of European Society of Human Reproduction and Embryology,2023)

CHAPTER 2:
INFERTILITY EVALUATION

2.1 Principles of care

1. Couples who experience problems in conceiving and seeking fertility treatment should be seen together because both partners are affected by decisions surrounding investigation and treatment
2. People should have the opportunity to make informed decisions regarding their care and treatment. Verbal informed consent should be taken
3. Counseling should be offered before, during and after investigation and treatment, irrespective of the outcome of these procedures

2.2 Key information to be provided

1. People who are concerned about their fertility should be informed that over 80% of couples in the general population will conceive within 1 year if:
   - The woman is aged under 36 years and
   - They do not use contraception and have regular sexual intercourse
2. Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate over 90%)
3. People who are concerned about their fertility should be informed that vaginal sexual intercourse every 2 to 3 days optimizes the chance of pregnancy
4. Women who are trying to become pregnant should be informed that drinking no more than 1 or 2 units of alcohol once or twice per week and avoiding episodes of intoxication reduces the risk of harming a developing fetus.
5. Women who smoke should be informed that this is likely to reduce their fertility

   Women should be informed that passive smoking is likely to affect their chance of conceiving. Men who smoke should be informed that there is an association between smoking and reduced semen quality
6. Women who have a BMI of 30 or over and who are not ovulating should be informed that losing weight is likely to increase their chance of conception

- Women who have a BMI of less than 19 and who have irregular menstruation or are not menstruating should be advised that increasing body weight is likely to improve their chance of conception
- Men who have a BMI of 30 or over should be informed that they are likely to have reduced fertility

7. Men should be informed that there is an association between elevated scrotal temperature and reduced semen quality
8. Women intending to become pregnant should be informed that dietary supplementation with folic acid 2 to 3 months before conception and up to 12 weeks' gestation reduces the risk of having a baby with neural tube defects.

2.3 The pre-evaluation requirements in the management of infertility are

- A respectful care approach
- An appreciation of cultural and social customs (taboos)
- An understanding of physiology and pathology of reproduction
- A knowledge of national guidelines

2.4 Investigation of fertility problems and management

- Couples who experience problems in conceiving should be seen together
- All the health care workers should identify the infertile couples and offer timely evaluation (Table 2) and referral to higher centers for treatment.
- The general medical officer should initiate infertility evaluation like detailed history taking and examination. The basic evaluation of infertility can be carried out by a general medical officer and should then refer to a Gynecologist for further management depending on the facilities available at the referral center.

There is strong recommendation that women older than 35 years receive an expedited infertility evaluation and undergo treatment after 6 months of failed attempts to conceive or earlier, if clinically indicated

Table 2: When to evaluate couple for infertility

When to evaluate	Criteria
1. Initiate evaluation after 12 months of unprotected and frequent intercourse:	• Women under age 35 years without risk factors for infertility
2. Initiate evaluation after 6 months of unprotected and frequent intercourse:	• Women age 35 to 40 years
3. Initiate evaluation upon presentation despite less than 6 months of unprotected and frequent intercourse:	• Women over age 40 years • Women with oligomenorrhea/amenorrhea • Women with a history of chemotherapy, radiation therapy, or advanced stage endometriosis • Women with known or suspected uterine/ tubal disease • Women whose male partner has a history of groin or testicular surgery, adult mumps, impotence or other sexual dysfunction, chemotherapy and/or radiation, or a history of subfertility with another partner

2.5 Management of female infertility

2.5.1 Counseling and consultation

The infertile couple should be seen together in a quiet and relaxed atmosphere with adequate time for discussion. A simple explanation of the basic physiology of reproduction and factors that may affect fertility should be given to the couple and the proposed investigations are discussed. They should be reassured that feelings of guilt or blame for inability to bear a child are unfounded. They should also understand that infertility is a shared problem and not of an individual. Counseling helps alleviate anxiety brought on by infertility.

2.5.2 History taking

Female	Male
General • Marriage history (number and duration of marriages) • Duration of infertility • Past use of contraception • PID following abortion/delivery • History of diabetes, thyroid diseases, TB and syphilis, HIV etc • Past history of pelvic surgery, any chronic pelvic pain, debilitating diseases • Abuse of alcohol and tobacco • Exposure to toxins • Intake of drugs like phenothiazines, antihypertensive and antidepressants	**General** • Ask whether puberty was delayed. • Ask for past history of TB, mumps, gonorrhea, urethritis or any trauma to the perineal region and surgery for hernia and varicocele • History of diabetes, thyroid diseases, TB, syphilis, and HIV etc.
Menstrual History • Menarche • Whether cycles are regular • Amount and duration of bleeding during menstruation • Presence or absence of dysmenorrhoea	**Drug history** • Any type of substance abuse? • Taking excessive alcohol? • Exposed to any toxins? • Excessive smoking? • Exposure to radiation, excessive heat
Obstetric and gynecological history in case of secondary infertility • Gravida, para, abortion, number of living children, mode of delivery • Number of pregnancies • Number of live births and number of living children • Number of abortions (at which months?) • Last childbirth or abortion	

Sexual history

- Careful and tactful inquiry about the nature and frequency of the couple's sexual intercourse is essential. When possible, any difficulties should be resolved before embarking on further investigations. In some, this resolution after careful counseling may be all that is needed for a successful pregnancy.
- Following conditions must be ruled out: impotency, retrograde ejaculation, vaginismus and dyspareunia.

2.5.3 Clinical examination

Female	Male
General • Assess general condition, BMI, thyroid abnormalities • Features of hyperandrogenism (Acne,hirsutism) and signs of virilization (masculine features like male voice, abnormal hair growth and male pattern distribution of hair)	**General Examination** • BMI, thyroid abnormalities • Presence of gynaecomastia • Any abnormal appearance or abnormal fat distribution • Features of Cushing's syndrome • Measure BP in erect and supine postures • Men with supine hypotension suffer from impotence.
Breast Examination • Tanner stage of breast	
Pelvic Examination • Conduct pelvic exam to assess for any congenital malformation, inflammations, and features of endometriosis	**Genital examination:** • Penile anomaly (Hypospadias) • Testis: consistency, size, any hydrocele or varicocele present • Cryptorchidism • Look for secondary sexual characteristics • Adreno-genital syndrome • Varicocele • Palpation in supine position • Palpation in erect position • Valsalva Maneuver

2.5.4 Investigation of fertility problems and management

Semen Analysis

- The usual initial investigation of the couple begins with semen analysis. The man is asked to abstain from sexual intercourse for 2-5 days and then to produce a semen sample by masturbation and collect it into a clean dry container. Collect the sample in the laboratory as far as possible or reach the sample to the Lab within half an hour and keep it at body temperature
- Semen analysis should be done in a designated laboratory. No alcohol should be used for cleaning in a semen analysis lab.
- Standard form is attached in the annexure (1) to give semen reports by all labs in the country so that there is uniformity in reporting
- If the result of the first semen analysis is abnormal, a repeat test should be offered in one month
- Abnormal semen parameters on treatment should complete the treatment first and then undergo semen analysis after 3 months.

Investigations for both the partners

- HIV screening, Hep B, Hep C, TPHA (screening is done for PMTCT with pretest and post test counseling)

Investigation for female factors

It is mandatory to undertake seminal fluid analysis before investigating the female.

1. **Ovarian reserve testing**
   - Use a woman's age as an initial predictor of her overall chance of success
   - Use one of the following to measure ovarian reserve
     - » Total antral follicle count(count of less than or equal to 4 for a low reserve/ response) where facilities are available
     - » Day 2 Follicle-stimulating hormone (greater than 8.9 IU/l for a low reserve/response) where facilities are available
     - » Anti-Müllerian hormone (AMH) for women more than 35 years (less than or equal to 5.4 pmol/l for a low reserve/ response) where facilities are available

2. **Tubal Factors and uterine factors**
    - **Ultrasound abdomen and pelvis** to assess the uterus and adnexa
    - **HSG (hysterosalpingogram):** Should be done between day 7 and 9 of menstruation to establish tubal patency. It can also reveal submucous fibroids and polyps inside the uterine cavity. Advise the woman to seek an appointment from the radiology department as soon as her menstruation starts.
    - **Laparoscopy:** It is usually indicated if there is abnormal finding in HSG such as a tubal block or inconclusive report. If there is suspected pelvic pathology, it should be done after the menstruation stops.
    - **Hysteroscopy:** This is indicated when there is suspected uterine or tubal pathology.
    - **SIS (saline infusion sonogram):** This is an ultrasound procedure. Principles are the same as HSG and comparable in diagnostic capacity
    - **Endometrial Biopsy or sampling:** where pelvic tuberculosis is suspected before ART

3. **Hormonal Assays.**

Female with Irregular cycle or amenorrhea to rule out the causes

- TFT (Suspected thyroid disease)
- Serum Prolactin (Early morning sample)
- FSH,LH (day 2 of the menstrual cycle)
- Luteal phase deficiency (Progesterone measurement on day 21 of menstrual cycle)

4. **Karyotyping**
    - In presence of primary amenorrhea, primary ovarian insufficiency and suspected chromosomal anomalies.

Investigation for male factors

1. **Ultrasound:** Ultrasound of scrotum in suspected scrotal pathologies
2. **Hormonal Assays:**
    - Serum Total testosterone (For primary testicular failure, erectile dysfunction, decreased libido or features of hypogonadotropic hypogonadism)

- Serum Prolactin: (For oligoasthenospermia)
- Follicle stimulating hormone (FSH),Luteinizing Hormone (LH) (For abnormal semen reports

  (For interpretation of FSH, LH, testosterone ; refer Table 3)

3. Urinary sediment for spermatozoa

- In suspected retrograde ejaculation

Table 3:

	Severely Impaired Spermatogenesis	Obstructive Azoospermia	Hypogonadotropic Hypogonadism
LH	↑ or Nl	Nl	↓
FSH	↑	Nl	↓
Testosterone	↓ or Nl	Nl	↓

4. Karyotyping

It must be done in males with azoospermia or severe oligospermia to rule out chromosomal disorders.

5. Testicular biopsy

- In azoospermia with normal testicular volume
- Teratospermia/asthenozoospermia

CHAPTER 3: TREATMENT

3.1 Treatment of Female Infertility

3.1.1 For anovulatory cycles: Ovulation induction

- Give Clomiphene citrate for a maximum of 6 cycles.
- Start tablet Clomiphene citrate on day 2 or 3 of the menstrual cycle for 5 days
- Dosage 50 mg - 150 mg daily for 5 days depending on the response
- If the women do not conceive with Clomiphene citrate (3 cycles), or if endometrium thickness remains less than 7 mm, shift to tablet letrozole 2.5 to 5 mg daily for 5 days
- HCG Injection (5000-10000 IU I/M or SC) may be given when the follicle size is 18 to 20 mm to trigger ovulation.
- FSH Injections is the next drug for ovulation induction if there is no response to clomiphene citrate or Letrozole. It is usually given with HCG Injection.
- For PCOS , Clomiphene citrate and Metformin can be given Tablet metformin 500 mg twice daily should be given
- Weight loss of 5-10% is advised to all obese women.

3.1.2 Tubal Factors

Anti- inflammatory and antibiotics or surgery (adhesiolysis or reconstructive surgery)to be done . If hydrosalpinx is present, it should be removed before any kind of infertility treatment including IVF.

3.1.3 Uterine factor: Surgery is done either to correct septate uterus or remove submucosal myomas and adhesion

3.1.4 Cervical factors: Treat cervico-vaginitis if present either with cryotherapy or antibiotics. Intrauterine insemination is advised.

3.1.5 Hypothyroidism: Can be treated with thyroxine replacement therapy.

3.1.6 Hyperprolactinemia: Bromocriptine (2.5 mg daily at bedtime)/ cabergoline (2.5 mg twice weekly) is used. Rarely surgery is needed.

TABLE 4. Summary of Investigation and treatment for Female Infertility

Cause	Investigation	Treatment
Ovulatory disorders	Ovarian reserve • AFC • AMH Endocrine tests • FSH • TFT Monitoring of ovulation • Ultrasound monitoring or • Mid-luteal progesterone measurement (> 3ng/ml suggestive of ovulation) Endometrial biopsy • Prior to IUI or IVF procedure.	• Correct thyroid abnormalities, diabetes, etc • Ovulation inductions
Hyperprolactinaemia	• Serum prolactin assay • Pituitary scan • Visual field examination	• Bromocriptine/ cabergoline Pituitary surgery
Tubal/ uterine factors	• Hysterosalpingography • Hysterosalpingo-contrast-sonography (HyCoSy) or SIS. • Laparoscopy • Hysteroscopy	• Treatment of PID, • Corrective surgery, • Microsurgery, • IVF
Cervical factors	• Post coital test • The post-coital test is not recommended	• Antibiotics, • Intrauterine • Insemination
Endometriosis	• Laparoscopy • Direct visualization and staging of endometriosis	• Surgical treatment, Ovulation induction, IVF
Unexplained Infertility	• All investigations done and found normal	• Reassurance, Ovulation induction with IUI,

3.2 Treatment of Male infertility

Male infertility is difficult to treat, because the cause cannot be recognized easily and it is difficult to study the response. All treatments to increase spermatogenesis take 3 months to give results (74 days for spermatogenesis and 10-14 days to travel through the epididymis).

In the interpretation of semen analysis, semen parameters are highly variable biological measures and may vary substantially from each ejaculate to ejaculate.If first semen analysis has abnormal parameters, second semen analysis should be ideally obtained one month apart.

1. **Lifestyle modifications.**
   - General measures such as maintenance of optimal body weight, avoidance of hot baths, tight underwear, and excess tobacco and alcohol consumption may improve sperm motility
   - Ongoing use of anabolic steroids suppresses spermatogenesis and interferes with fertility
   - Treatment is based on the type of SA abnormality.

2. **Oligospermia (< 10 million/ml)**
   - >5 million /ml offer IUI (6 cycles) and if failed IVF (this service is at present not available in the country).

3. **Severe Oligospermia (< 5 million /ml)**
   - Initial examination to look for Testicular volume (look for testicular atrophy).
   - FSH and Testosterone level .
   - If low FSH with normal testicular volume - trial of clomiphene citrate 50 mg once for 3 months .
   - If increased FSH level and testicular atrophy - send for Karyotype (not available in the country) to rule out Klinefelter syndrome or Y microdeletion.
   - Offer IVF(In vitro fertilization) or ICSI(Intracytoplasmic sperm injection).

4. Azoospermia

- There are two types of azoospermia .The history, physical examination and hormonal studies can help differentiate obstructive from non-obstructive azoospermia.
- **Obstructive azoospermia**
  - Men have normal testis volume (12.5 to 19 ml)
  - FSH <7.6
  - Semen volume < 0.5 or 1.0 mL
  - Treatment will be surgery- microsurgical reconstruction of Obstruction or Sperm retrieval

- **Non Obstructive azoospermia(NOA)**
  - Men have low testes volume , and high FSH and LH levels.
  - They should undergo genetic testing (karyotype and Y microdeletion)
  - Treatment options are microTESE (Microsurgical testicular sperm extraction) and ICSI (Both these facilities are not available in the country).

3.3 Unexplained infertility (UI)

Approximately 15 % of infertile couples are considered to experience "unexplained infertility" (UI). This controversial diagnosis is made when no abnormalities of the female and male reproductive systems are identified. UI is inevitably a diagnosis by exclusion, following otherwise "standard" investigations.

The International Committee for Monitoring Assisted Reproductive Technologies (ICMART) defined UI as "infertility in couples with apparently normal ovarian function, fallopian tubes, uterus, cervix and pelvis and with adequate coital frequency; and apparently normal testicular function, genitourinary anatomy and a normal ejaculate.

Treatment

Expectant management

- Reassure
- A healthy diet and regular exercise, supported by behavioral therapy, when necessary, are recommended.
- Advise women with unexplained infertility who are having regular unprotected sexual intercourse to try to conceive for a total of 1 year if less than 35 years.

Active management

- Provide IUI with ovarian stimulation (clomiphene citrate or letrozole or gonadotropins) for 6 cycles
- To avoid multiple pregnancies and OHSS, care is needed by using gonadotrophin treatment only in a low-dose regimen with adequate monitoring
- IVF is probably not recommended over IUI with ovarian stimulation in couples with unexplained infertility

CHAPTER 4:
ASSISTED REPRODUCTIVE TECHNOLOGY (ART)

4.1 Definition

Any treatment or procedure that involves in-vitro handling of human oocytes or sperms or embryos for the purpose of establishing pregnancy, is known as ART.

4.2 Intrauterine insemination (IUI)

- Instrumental deposition of processed and enriched sperms into the uterine cavity.
- *Only legally* recognized partner's sperm will be used.
- Indications
- Mild to moderately abnormal semen parameters
  - » Oligozoospermia (sperm count 5-20 million/ml)
  - » Asthenospermia (less than 29%)
- Failure of ovulation induction (6 cycles)
- Cervical factor-cervical stenosis or poor cervical mucus production
- Male ejaculatory dysfunction
- Unexplained infertility

IUI (Intrauterine insemination) Procedure .

1. A semen analysis is done prior to starting the sperm preparation techniques
2. Two basic types of techniques are followed in the laboratory; Sperm wash and Swim up technique and Second is Density Gradient techniques.
3. Clients undergoing IUI should have OI (Ovulation Induction) and IUI form filled up by the respective treating gynecologist and handover to duty staff(nurse or technician) at the infertility clinic.
4. IUI should be carried out 36 hours after Inj HCG is given or after Ovulation is confirmed (can be confirmed by TVS prior to IUI).
5. The IUI procedure should be carried out in a separate IUI Room. The room should have a table equipped to position women in Dorsolithotomy position.

6. Patients should be asked to empty her urinary bladder.
7. She is placed in lithotomy or dorsal position
8. Insert a bivalve speculum and visualize the cervix.
9. Use a swab soaked in saline solution to cleanse the external OS.
10. Under direct visualization, the loaded IUI cannula with prepared sperm on an attached tuberculin syringe (.5 ml) is introduced into the cervical canal or uterine cavity (tenaculum is generally not required).
11. The content is slowly injected .
12. The patient is left in a supine position for 10 to 20 minutes.
13. Progesterone support after IUI is given up to 10 weeks in case of pregnancy.Inj hydroxyprogesterone 250 mg i/m weekly
14. Serum beta HCG or Urine pregnancy test should be done one week after the missed period.
15. 3 Cycles of IUI should be provided, after which if not conceived, other options of ART like IVF should be discussed with the couple.

4.3 IVF-ET (in vitro fertilization and embryo transfer)

(At present, IVF and ICSI services are not available in the country). However, it will be introduced in the near future.

IVF can be conventional or ICSI **(intracytoplasmic sperm injection)**

Indications

- Tubal damage/blockage
- Post tubal sterilization
- Endometriosis after failure with Ovulation inductions and IUI.
- Failed IUI
- Male infertility if sperm count after enrichment is 1-5 million
- No ovaries/ovum production in women, with normal uterus (using donor ova)

Steps in IVF-ET are

- Induction of multiple ovulations: this is done with Inj FSH/ Inj HMG and Inj HCG Follicles are aspirated (ovum retrieval), when follicular sizes are 17-18 mm. This is done under guidance of transvaginal ultrasound, under short GA in OT. Oocytes are incubated at 37 degrees in culture media for 6 hours to complete the maturation process. Where women cannot produce oocytes, donated ones are used.
- In vitro fertilization: Fresh sperms are collected 2-3 hours before and enriched (frozen sperms are also used) and put together with oocytes in a petri dish and incubated overnight. Fertilized ovum is allowed to develop up-to blastocyst stage.
- Embryo transfers into the uterus: Usually 2 embryos are transferred into the uterus nowadays. If more embryos have been produced, they are kept frozen for future use.

Follow up

- Patient is discharged after 24 hours with advice to rest for 3-4 days.
- She is given Progesterone support by parenteral or vaginal route for 8-10 weeks
- She must do a serum HCG after 12 days of transfer.
- An ultrasound (TVS) is done at 6-7 weeks to see whether the embryo is developing.
- Multiple pregnancy rate is 29-37% (twins: 29-32%, triplets: 2%)
- Success rate: 30-35% with 15 % take home baby.

ICSI

This is an IVF procedure in which a single sperm is injected into an oocyte. This is a treatment for severe male infertility.

Preparation of a female partner with ovulation induction, ovum retrieval, embryo transfer and progesterone support are the same as in IVF-ET.

4.4 Male and female recanalisation

Indications for recanalization are:

- Death of one or more children.
- Re-marriage after divorce or death of a spouse.

Contra- indications are

Male:

- Wife suffering from a medical condition that will be aggravated by pregnancy, endangering her life.
- Spouse has an irreversible infertility disorder.
- Client has bilateral testicular atrophy.

Female

- Client is over 40 years old
- She has medical or surgical conditions that will be aggravated by pregnancy.
- The available portion of tubes is less than 4 cm long or had fimbriectomy or damaged due to PID
- Spouse has an irreversible infertile condition

Note: Where IVF facility is available, recanalization is not advised.

CHAPTER 5:
INFERTILITY MANAGEMENT IN VARIOUS LEVELS OF HEALTH FACILITY IN BHUTAN

5.1 Summary of infertility management at various level of health facility in Bhutan

Services	Health Facility	Responsible health worker	Remarks
Good history taking(refer text)	All hospitals and PHCs	Clinicians	Refer to higher level
General examination including genital examination (refer text)	-Do-	Clinicians	Refer to higher level
Proper counseling and information on reproductive physiology	-Do-	Clinicians	Refer to higher level
Semen analysis	Hospitals	Lab Technicians/ Technologist	Where Lab facilities are present
Endometrial biopsy (D & C)	Hospitals	Gynecologists	Where there are gynecologists
Hysterosalpingogram (HSG)	Hospitals with radiologists	Radiologists	JDWNRH, Gelephu and Monggar
Diagnostic Laparoscopy and Dye test	Hospitals with Laparoscopy services	Gynecologists	Where gynecologist is present

Services	Health Facility	Responsible health worker	Remarks
Basic investigations like • Blood Grouping • VDRL/RPR • Screening for Tuberculosis • Ultrasound	Hospitals	Clinicians	Where lab and ultrasound facilities available
Hormone analysis	JDWNRH, ERRH, CRRH	Lab Technicians/ Technologists	
Gynecologists	NRH, RRH		
Surgical procedures	Hospitals	Gynecologists	Hospitals where Gynecologists are present
Ovulation induction and other Hormonal therapies	Hospitals	Gynecologists	Hospitals where Gynecologists are present
Intrauterine Insemination (IUI)	JDWNRH, CRRH, ERRH	Gynecologists and trained laboratory for IUI	NRH, RRH
Prevention of infertility by treating STI and RTI	All levels of health facility	Clinicians	Use STI manual

CHAPTER 6:
PREVENTION OF INFERTILITY

Following are some of the things you can do to prevent development of infertility:

6.1 Treatment of STI (Sexually Transmitted Infections) and other RTIs (Reproductive Tract Infections)

STIs are the leading cause of preventable infertility both in men and women. Levels of infertility may be influenced by differences in prevalence of STI, access to adequate health care for STIs, abortions and childbirth. Secondary infertility is especially decreased by access to adequate obstetric care.

6.2 Sequel of untreated STI

- Infertility
- PID
- Increased risk of ectopic pregnancy
- Mother to child transmission
- Repeated abortion/still births (syphilis)

6.3 Partner tracing

STI treatment is not complete without treatment of partner/partners, so, all the partners should be traced and treated at the same time.

For STI counseling and treatment, refer to the (National STI guideline).

6.4 Postpartum Sepsis

Women with puerperal sepsis are prone to uterine infection , infection of fallopian tubes leading to tubal blockage which can cause secondary infertility.

It can be prevented by

- Safe delivery with proper sterilization of instruments and ANC counseling
- Early recognition and treatment of infection in the postpartum period, ask about history of prolonged bleeding, foul smelling discharge, and fever and pain abdomen.

- Prompt evacuation of retained placental parts
- And proper management of prolonged rupture of membranes.

For further management of Puerperal Sepsis, refer to the National Midwifery Standards on Life-Saving Midwifery Practice Standard 5 on Puerperal Sepsis

6.5 Septic miscarriage

Septic miscarriage can be either spontaneous or induced. Timely treatment for incomplete abortion with antibiotics can prevent sepsis and related complications.
(For management refer to the National Abortion guidelines

ANNEXURE

1. Semen profile report

Name: Age: Date:
Reg/CID No: Referred by :
Sample collection method:

Container condition:
Abstinence
Spillage
Specimen production time
Specimen collection time
Specimen examination time
Specimen preserved at degree centigrade
Appearance
Volume
Self liquification time
Viscosity

Biochemical Examination
pH fructose

Microscopic examination

Sperm count millions/ml
Motility
Progressive
Immotile
Vitality

Sperm morphology
Normal
Head defect
Neck defect
Tail defect

Impression

Recommendation

NORMAL VALUES OF SEMEN ANALYSIS (WHO 2021)

Volume	1.4 (1.3 - 1.5) ml
Concentration	≥15 x 106/ml
Total Sperm Count per ejaculate	35-40 million (Volume * Concentration)
Total Motility	42% (40 - 43)
Progressive motility (after 1 hour of ejaculation)	30% (29-31)
Non-progressive motility	1%
Immotile	20% (19 - 20)
Vitality	54 %(50-56)
Morphology	≥4% normal
Leucocytes	<1x 106/ml
Agglutination	<50%

TERMINOLOGY IN SEMEN ANALYSIS

Aspermia: Absence of ejaculation

Azoospermia: Absence of spermatozoa in ejaculate even after centrifuging

Necrospermia: All spermatozoa are dead

Oligozoospermia: Total number of spermatozoa is less than 15 million/ml

Astenospermia: Progressive motility is less than normal

Teratospermia: Abnormal morphology is more than 4%

2. Intrauterine insemination report

Date: Referred by:

Patient's name: Age:

Partner's name: Age:

Sperm source:

Patient's registration/CID number:

Partner's registration/CID number:

Parameter	Value
Specimen Date	
Time Produced	
Volume	
Concentration (millions/ml)	
% Motility	
Clumping	
Viscosity (+/++)	
Cells (millions/ml)	
Method of preparation	
Preparation time	
Post wash concentration	
Post wash % motility	

Important note:

Advice:

Andrologist sign: consultant sign:

3. Ovulation Induction Form, Infertility Unit

Ovulation Induction Cycle.....

Name of patient:..... Age..... Reg No.....

LMP..... Indication.....

Ovulation induction done : Tab Clomiphene Citrate (100 mg)/Letrozole (2.5mg)

Followed by Injection Menogon (HMG) 75 IU/50 IM/SC daily from day 7 to 9 (given/not given)

Date	day of cycle	End. thickness	Follicles in left ovary (sizes)	Follicles in right ovary (sizes)	Done by
	2				
	8				
	12				
	14				

4. IUI Form, Infertility Unit

IUI cycle.....

Name:..... Age..... Reg No .....

LMP..... Indication.....

Ovulation induction done with: Tab Letrozole/Tab clomiphene citrate (day 2 to 6 day). Dose.....mg/day

Followed by Menogon (HMG) 75 IU/150 IM/SC daily from day 7 to 9 (given/ not given)

Date	Day of cycle	End. thickness	Follicles in left ovary (sizes)	Follicles in right ovary (sizes)	Done by
	2				
	8				
	12				
	14				

Date of HCG injection- Date of IUI:-

5. Side effects of medicine

Sl. No	Name of medicine	Side effects
1	Clomiphene (in 5-6 %)	Nausea, dizziness, allergic dermatitis, hair loss and visual disturbances. Stop treatment immediately if there are visual disturbances
2	Letrozole	Flushing, hypercholesterolemia, diaphoresis, nausea, vomiting, dizziness, arthralgia, and myalgia
3	Injection FSH	Acne, headache, abdominal pain, nausea, flatulence, ovarian hyperstimulation syndrome.
4	Injection HCG	Headache, fatigue, gynecomastia, mastalgia, ovarian hyperstimulation syndrome, hypersensitivity.

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Acknowledgement

The Department of Public Health, Ministry of Health would like to sincerely acknowledge following officials for carrying out the revision of the guideline;

1. Dr. Sonam Gyamtsho, OBGYN, JDWNRH
2. Dr. Gyem Dorji, Asst. Professor, KGUMSB
3. Dr. Sangay Tshering, OBGYN, JDWNRH
4. Dr. Nedup Gyeltshen, OBGYN, JDWNRH
5. Dr. Tshering Tamang, OBGYN, ERRH
6. Ms. Karma Tshering, UNFPA Country Office
7. Mr. Karma Galey, APO, DHS, MoH
8. Mr. Tshering Duba, Dy. Chief Pharmacist, DHS, MoH
9. Mr. Jamyang Tenzin, Lab Tech, CRRH
10. Ms. Sonam Zangmo, Lab Tech, JDWNRH
11. Mr. Karma Tenzin, Sr. PO, RMNHP
12. Ms. Tashi Tshomo,Sr. PO, RMNHP
13. Ms. Chimmi Dem, Sr. PO, RMNHP