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# Evidence based approach to concept of anovulatory infertility in Unani medicine: An update

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**Abstract**
Infertility has been a major medical and social paradigm since the dawn of human existence and women have always been the symbol of fertility. 10-15% of marriages prove to be childless, female factor are responsible for 40% of infertility cases in which anovulation accounts for 30%. The serious consequences of chronic anovulation are infertility and a greater risk for development of endometrial cancer. In the entire infertility factor, disorder of ovulation has the widest range of treatment armamentarium with the administration of ovulation inducing agents to achieve pregnancy rates without increase in untoward side effects. It has been mentioned in Unani encyclopedias that the cause of female infertility is decrease in the quantity of *mani* (ovum) i.e. oligo ovulation or anovulation; more over, the defect in ovum is attributed to *sue mizaj barid* which solidifies ovum leading to anovulatory infertility. Unani physicians recommended various formulations for the treatment of anovulatory infertility possessing the properties like *muqawwi rehm* (uterine tonics), *moaene hamal* (helpful in conception) and *mawallide mani* (ovulation inducing) which has to be used from 5$^{th}$ day of menstrual cycle (corresponds to ovulation inducing drugs). This shows that the concept of ovulation induction was well known to Unani physicians. These drugs are known to contain phytohormones and may induce ovulation by maintaining hormonal balance.
The aim of this paper is to review the etiopathogenesis, diagnostic and curative aspect present in Unani literature with simultaneous correlation with modern literature and to develop evidence based approach through research in Unani medicine in the management of Anovulatory infertility.

**Keywords:** infertility, anovulation, conception, phytohormones, unani medicine

## Introduction
Ovulation is the most important aspect of female fertility [1]. Normal ovulation requires coordination of the menstrual cycle at central hypothalamus pituitary axis, the feedback signals and the local response within the ovaries [2]. Any disruption to these factors at any level may result in anovulation [3]. Anovulation is the most common etiologic factor of infertility [4, 5] which accounts for approximately 30% of all cases [6]. The causes of anovulation include hypothalamic failure, hyperprolactinaemia, polycystic ovarian syndrome, premature ovarian failure, subclinical hypothyroidism, adrenal failure and obesity [7]; out of these disorders, polycystic ovarian syndrome is the commonest, easily diagnosed and most treatable cause of anovulatory infertility [8] accounting for 75% of cases. Disorders of anovulation presents in variety of clinical scenarios including amenorrhoea, oligomenorrhoea, hirsutism, obesity and infertility. The serious consequences of chronic anovulation are infertility and risk for the development of endometrial cancer [7].

## Methods
For Unani concept of anovulatory infertility, available authentic text of Unani Medicine was searched. Literature was also searched on PubMed/Google Scholar with the keywords; Herbs for ovulation induction, Unani medicine effective in ovulation induction, alternative medicine for anovulatory infertility etc.

## Unani Concept
Renowned Unani physician, *Al Majoosi* mentioned the concept of ovulation centuries ago. He states that an ovary produces a follicle which secretes ovum, the later reaches the uterine cavity through the fallopian tubes [9]. The ancient Egyptians describe infertility as a disruption in the continuity between the reproductive organs and digestive tract and diagnosis was made on physical examination [10]. Hippocrates (460-370 BC) described several causes of infertility & potential therapies. Galen (A.D 131-201) believed that there was a mixing of male and female semen with the formation of conception [11].

## Factors essential for fertility
- Age: Fertility rate is more in the age group of 15-40 years [12].
- Temperament: Uterus and ovaries must have normal temperament (hot & moist) & firm in consistency; even the temperament of women should be *har* (hot) & *ratab* (moist) as *hararat* helps in absorption of *mani* and *rutubat* infiltrates *mani* in *tajaweefe rehm* [13].

- Menstruation: Regular cyclic menstruation is essential for conception.
- Use of fertile period: Intercourse immediately following the menstruation tends to increase the fertility as external os is widely open, capable to receive the *mani* (sperm) and *aneque rehm* remains uneven.
- Balance to be maintained in nutrition, emotions & intercourse [12].

**Anovulation**

In classical Unani literature, the description of anovulation is mentioned under the headings of *uqr* (infertility), which is defined as inability to conceive either due to defect in *mani* (sperm) of male partner or *mani (*ovum) of female partner or both [4, 14, 15]. *Toole ehtebase mani* (chronic anovulation) is mainly caused by *sue mizaj* (abnormal temperament) either hot, cold, dry, moist or intake of *tursh ghiza* (sour food) which causes excessive coldness and dryness [14].

**Etiopathogenesis**

1. **Ovaries:** Any sort of defect in ovaries leads to faulty production of ovum, which is either due to *qillate maddae manwia* (oligo-ovulation/anovulation) or *fasade mani* (dysovulation).[16] Even when the ovaries are extremely cold it fails to produce ovum [12]. In PCOD, *sue mizaj barid* of the liver causes dominance of *khilt balgham*, as liver is unable to convert chyme into blood, instead it converts it into *balgham lazij*. One of the abnormal forms of *balgham* is *balgham mayi* which is thinner in consistency and can accumulate in sacs to form cysts in ovaries [17].
2. **Menstruation:** Irregular and scanty menstruation causes infertility, as uterine vessels are filled *with* viscous *phlegm* which weakens the *quwwate jaziba* of *rehm* (retentive power of uterus*)* as a result ovum is unable to retain with in the uterus and grows further. Even excessive menstruation [12] or absence of menstruation prevents conception [12, 16]. Women with frequent & scanty menstruation tends to be infertile secondary to either *qillate dam* (anemia*)* or *kasafate urooqe rehm* (luteal phase defect), as both this conditions are unfavourable for conception [12].
3. ***Sue mjzaj* (Altered temperament):** The defect in ovum is attributed to *sue mizaj mukhtalif* of *quwwate tauwleede mani*, which is mainly due to *sue mizaj barid* [9, 13, 14, 15, 16].
   - ***Sue mizaj barid*:** *Baroodat* causes obstruction in the flow of ovum and menstrual blood towards the uterus.[9] It solidifies ovum [14, 18] as a result follicle formed in ovaries is less in amount and fails to grow further [9]. The cause of *sue mizaj barid* is either over eating [15] or excessive intake of cold items in diet [12, 14]. Also, *sue mizaj barid* due to prolonged abstinence from intercourse may lead to female infertility [9].
   - ***Sue mizaj haar*:** It destroy *mani* [9, 15, 18] as ovum is unable to get proper nutrition [9] which leads to *fasade mani* (defective folliculogenesis) [12, 19].
   - ***Sue mizaj ratab*:** It causes weakness of *quwate jaziba* of *rehm*, as a result *mani* is unable to retain with in the uterus leading to *uqr* due to reduced endometrial receptivity [12, 19].
   - ***Sue mizaj yabis*:** It destroy *mani* [15, 16, 17] and causes *fasade mani* leading to *uqr*.[9] It occurs due to excessive use of those drugs which create dryness in the body [19].
4. **Age:** Women can able to get pregnant until she is menstruating; [9] if a woman get pregnant <15 years of age, it endangers her life due to hypoplastic uterus and old age women tends to be infertile as the quality of ovum is impaired [12]. Women's fertility decline rapidly after 37 years due to decrease in egg quality [20].
5. **Body weight:** Lean woman is infertile as ovum is unable to get proper nutrition [12] and no excreta are retained following the metabolism resulting in no ovulation. [21] An obese woman tends to be infertile mainly due to displacement of uterus and obstruction in the flow of ovum and menstrual blood toward the uterus.[9] Excessive weight loss or weight gain hamper the fertility as ovarian function depends on weight. There is a clear correlation between body fat and reproductive function at both ends of weight spectrum. Low body fat causes hypothalamic hypogonadism [22], while central body fat results in insulin resistance & ovarian dysfunction in PCOD.[22, 23]High BMI increases Sr. leptin & decreases Sr. adeponectin level which inhibits ovarian steroidogenesis & increases circulating insulin level which in turn enhances LH and androgens; even peripheral conversion of androgens to estrogen in adipose tissue inhibits gonadotropin secretion.[24] Hippocrates[9] states that a woman seeking conception should reduce her weight [9, 12, 15].
6. **Addiction:** Alcoholic and addicted woman fails to conceive as their temperament becomes more moist. In addition an addicted woman is infertile as the quality of ovum is impaired [12, 13]. Increased rate of menstrual irregularities & infertility are associated with increased alcohol consumption, as it exerts its effects by increasing estrogen & testosterone levels, and this testosterone is a well-known suppressor of the hypothalamic–pituitary unit, resulting in decrease GnRH secretion leading to anovulation. Even, alcohol may disrupt reproductive cyclicity by diminishing IGF–1, and the ability of IGF–1 to increase LH was blocked by alcohol [12]. Fertility society of Australia recommended that women trying to conceive & pregnant should avoid drinking alcohol as it effects fertility [12, 16].
7. **Psychological:** Stress, fear and shock leads to *uqr* as *mani* fails to form in *azae mani* (ovaries); besides, women who are in deep stress tends to be infertile.[12] Stress makes the adrenal gland to produce glucocorticoids, which inhibit the GnRH production from hypothalamus. Researchers have now found that glucocorticoids also boost hypothalamic GnIH production which not only suppresses GnRH production but directly inhibits pituitary secretion of sex hormones, thereby suppressing the entire reproductive system [27].
8. **Others:** *Zoaf dimagh wa meda wa hazam wa jigar* and *soul quinya* [15, 19].

   *Zoaf dimagh* (hypothalamus dysfunction) may cause reduced secretion of gonadotropin from the pituitary leads to loss of ovarian hormone production resulting in anovulation [22]. *Zoaf meda wa hazam* (Irritable bowel disease-IBD) such as crohn's disease causes severe inflammation in the small intestine, can sometimes affect

the normal functioning of the ovaries. Research studies have found that women with active Crohn's may have lower levels of a hormone (AMH) associated with 'ovarian reserve' especially if they are over 30 years. IBD inflammation can also cause adhesions that affect the fallopian tubes [28]. In *zoaf jigar* (liver dysfunction), the study showed that oestrogen receptors in the liver are critical for maintaining fertility, and that the expression of these receptors is under the control of dietary amino acids, the building blocks of proteins. Mice on a calorie-restricted diet and those lacking oestrogen receptors in their livers showed a decline in an important hormone known as IGF-1. The scientists showed that the blood levels of the hormone dropped to levels inadequate for the correct growth of the lining of the mice's uterus and normal progression of the oestrous cycle. However, when calorie-restricted mice were fed with more protein, their reproductive cycles returns to normal [29]. In *soul quinya* (anemia), studies have shown that women who do not get sufficient amounts of iron may suffer anovulation due to poor egg health following the reduced $O_2$ supply to ovaries, which can inhibit pregnancy at a rate 60% higher than those with sufficient iron stores in their blood. So, depletes iron store in anemia due to insufficient RBC's may cause infertility due to unviable oocyte [30].

9. **Congenital:** *Khusiyatur rehm ka naqis ya chota hona* [19, 31] (premature ovarian failure/streak gonads).

**Diagnosis**

It is made on the basis of history, clinical features & certain test.

1. *Sue mizaj barid*: H/o irregular menstruation with scanty flow, menstrual blood is red in colour and thin in consistency [21]; scanty pubic hair, white and cold skin [14, 19]. *Nabz* is *sagheer bate* and *mutfawit* [32] and urine is whitish in colour. [18]
2. *Sue mizaj haar*: H/o foul smell menstrual blood [14] which is scanty in flow, [15] black in colour [13, 21] and thick in consistency; dense pubic hair, thin and pale skin[21]*Nabz* is *zaeef*[32].
3. *Sue mizaj yabis*: H/o delayed and scanty menses with general weakness, dry vagina, thin skin [21]; *Nabz* is *sulb*, *murtaish* and *mutashannij* [32].
4. *Sue mizaj ratab*: H/o abnormal discharge of *ratoobat* from uterus [21, 14] and abortion [14]. *Nabz* become *laiyan*, urine is white in colour and thin in consistency [14].
5. Dominance of *khitle balgham*, *safra* or *sauda*, leads to abnormal discharge of *ratoobat* from the uterus which may be whitish or yellowish or blackish in colour [21].

**Test for detection of fertility**

1. Pour urine of both male and female partners on root of *kahu* and if the root dries up, then the particular partner is defective.
2. Acquire seven grains each of wheat, barley and broad bean; put in earthen pot and instruct both the partners to urinate on it and if the grains germinates with urine, then the defect is not in that particular partner [9, 15]. In 1963, the laboratory test showed that urine of pregnant women did cause the seeds to sprout. The seeds probably started to grow due to the elevated levels of estrogens in urine which stimulate growth [33].

**Treatment**

In Unani system of medicine, principles of treatment includes

- Correction of *sue mizaj* (abnormal temperament) with *tadbeer*, *ghiza* and *dawa*.
- *Tanqia badan* with *mus'hilaat*,
- Maintaining body weight with *tadbeer*, *ghiza* and *dawa*,
- Use of *mudire haiz* (emmenagogue) drugs and
- Use of *mwallide mani* (ovulation inducing) drugs. [9, 12,13, 15, 16, 18].

***Mujarib nuskhas* for *mawalide mani* (ovulation induction) in anovulatory infertility**

- Ovulation inducing drugs should be used after menses [9, 12, 13, 15, 16, 18].

**Oral**

- *Gule dhawa*, *gule nilofer*, *baikh piyababsa* and *baikh asgand*; each in equal quantity are finely powdered and used 12 g with milk after menses [16, 31].
- Fine powder of *kayephal* and sugar in equal quantity, used in a dose of one fist for 3 days after menses.
- Powder of *mushk* 250 mg, *afiyoon*, *jozbua* and *zafran* each 1 g, *barg qinnab* 2 g, *qaranfal qalan* 4 no's and *foofal gujrati* 3 no's are mixed in *qand syah kohna* 5.25 g*; qurs* are prepared & used for 3 days after menses.
- *Qurs* weighing 62.5 mg are prepared from powder of *murr makki* and *naushadar*, used one *qurs* daily during menses.
- *Musli siyah wa safaid*, *gokhru*, *tukhm otangan* and *post baikh saimbhal*; each 24 g in powder form & used with cow's milk for 5 days after menses [16].
- Use one tablet of *habe hamal* with *majoon mocharas* 12 g in morning; two tablet of *habe marwareed* with *arq amber* 36 g, *arq gauzaban* 84 g and *misri* 24 g in evening after menses [31].

**Local**

**1. *Humool* (pessary)**

- *Qurs* prepared from *koknar*, *mazu*, *dhatoora* and *qand syah kohna*, used for 2 days during menses and for 1 day after menses.
- *Jundbedastar*, 4.5 g, *shibe yamani*, *zafran* and *lesanul asafeer*, each 3.5 g, *ood* 1.75 g, *mushk* 750 mg are finely powdered and mixed with *shahed*; used for 3 days during menses [16].

**2. *Dhooni* (fumigation)**

- *Hartal*, *jozul saru* and *miyasaela* for 3 days [14].
- *Zareekh ahmar* and *jozul saru* are doughed in *miyasaela*, advice to pursue sexual contact after dhooni [12, 13].
- Prepare *qurs* of *miyasaela* and *habbul ghar* in *shahed* [12].

**3. *Huqna* (enema)**

- Decoction of *qashoor qand* and *nagarmotha*, each 100g, *murr makki* 70g, water 1 litre, used in the form of *huqna* in *rehm* after menses [9].

**Nutritional approach to fertility**


**Fig 1**

**Diet recommended**

Use diet rich in fish as it supplies the essential omega 3 fatty acids which help in the production of hormones and thus regularize the menstruation and it also provides Vitamin $B_{12}$, Vitamin D, zinc, and selenium. Grains in their natural form are filled with fiber, vitamins, and immune supporting properties e.g. whole wheat bread, rice and brown rice. Fiber helps to regulate the blood sugar levels, reduces incidence of PCOS and promotes hormonal balance. e.g. green leafy vegetables, lentils, beans and fruits. Dark leafy vegetables provide Iron, Folic acid, Vitamin $B_6$ & Vitamin E. Fruit contains Vitamin C, flavonoids and variety of antioxidants. Eggs supply proteins, Vitamin D & Vitamin $B_{12}$. Nuts and seeds contain protein, omega 3fatty acids, zinc &Vitamin E.

**Diet restricted**

Avoid processed and refined white foods such as white bread and rice; processed soy foods such as soy milk, burgers, chips, meats, and cheese; refined sugar or fruit juices, red meat, non-organic chicken**,** alcohol, caffeine etc [34].

**Unani medicine effective for ovulation induction**

Many single drugs and compound formulations are mentioned in classical Unani text for induction of ovulation, besides only some of them have been scientifically evaluated.

1. **Flaxseed/*Alsi* (*Linum usitatissimum*) Figure-2:** It is a powerful herbal remedy for ovulation as it contains lignans which balances hormones and regulates the menstrual cycle.

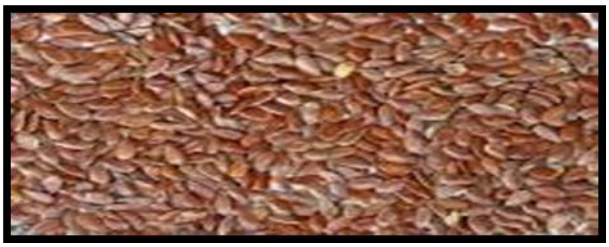

**Fig 2:** *Linum usitatissimum*

2. **Chaste berry/*Shambhalu* (*Vitex agnus-castus*) Figure-3:** This is one of the most effective herbs for inducing ovulation by balancing the hormones as documented by clinical trials which demonstrate the increased mid-luteal progesterone [35].

**Fig 3:** *Vitex agnus-castus*

3. **Red clover/*Ispast* (*Trifolium pretense)* Figure-4:** It contains is of lavones which enhances fertility by maintaining hormonal balance.

**Fig 4:** *Trifolium pretense*

4. **Nettle leaf/*Anjura (Urtica Dioica)* Figure-5:** It is one amongst the most effective herb for ovulation as it is rich in antioxidants, calcium, vitamins A, C, D and K, potassium, phosphorous, iron and sulphur [36].

**Fig 5**: *Urtica Dioica*

5. ***Satavar (Asparagus recemosus* Wild) -Figure 6:** It is effective for ovulation induction, as clinical study conducted on patients with anovulatory infertility showed that the ovulatory rate was 25% & 30%, but the conception rate was nil. This effect is attributed to the presence of phytoestrogens- steroidal saponins in this drug which exert hormone like action in the body [37].

**Fig 6:** *Asparagus recemosus* Wild

**Fig 7:** *Withania somnifera* Linn

**Fig 8:** *Anogeissus latifolia*.

**Fig 9:** *Nymphaea alba* Linn

**Fig 10:** *Barleria prionitis* Linn

6. **Gule dhawa (Anogeissus latifolia), Gule nilofer (Nymphaea alba Linn), Baikh piyabansa (Barleria prionitis Linn) and Baikh asgand (Withania somnifera Linn) Figure 7-10:** Each drug in equal quantity are finely powdered and used 12 g with milk after menses. Clinical study conducted for ovulation induction in patients with anovulatory infertility using this formulation showed that ovulatory rate was 40%, 35.3% and 68.8% in 1st, 2nd and 3rd cycle and conception rate was 10% and 18.8% in 1st and 3rd cycle respectively. Hence, this formulation can be used as an alternate therapy for ovulation induction [38].

**Fig 11:** *Trachyspermum ammi* Linn

**Fig 12:** *Pimpinella anisum* Linn

**Fig 13:** *Apium graveolens* Linn

**Fig 14:** *Trigonella foenum graecum*

**Fig 15:** *Valeriana wallichi* DC

7. **Tukhme karafs (Apium graveolans), Anisoon (Pimpinella anisum), Ajwain desi (Ptychotis ajowan), Tukhme hulba (Trigonella foenum), Asaroon (Valeriana wallichii) Figure 11-15:** 12.5 g of these drugs were administered orally in decoction form twice daily for two consecutive months. Clinical study was conducted to evaluate the efficacy of this compound formulation on infertility among obese women demonstrated that Unani formulation was helpful in conception probably by weight reduction, menstrual regulation and ovulation as 10% patients conceived after 2 months of completion of study. Pharmacological studies suggest that the ingredients of this formulation act as insulin sensitizer, hypolipidemic, diuretic, emmenagogue and are known to contain phytohormones like flavonoids, saponins, glycosides and obesity suppressing active substances (diosgenin and camphene) [39].

## Conclusion

Anovulation is the most common cause of infertility, and the available treatment in conventional medicine includes ovulation induction with hormonal pills which though effective but has its own side effects & are contraindicated in patients with hypertension, deep venous thrombosis, heart diseases, chronic renal & liver diseases. Hence, alternative medicine can be tested which are easily available, cost effective & free from side effects. Herbal drugs are safe with lesser side effects and presence of multiple active compounds in them provides a potentiating effect such as they enhances the immunity of the body, regularize the menstrual cycle and induces the ovulation by maintaining hormonal balance [40]. Lifestyle modification with diet & exercise are to be recommended as a first line of management of anovulation especially in obese infertile women. Effective management is available in Unani system of medicine which can be applied in day to day clinical practice. Despite of several Unani drugs mentioned, experimental studies have been conducted on few to explore pharmacological activities of these drugs and are associated with diverse limitations. Furthermore, well-designed randomized controlled trial with double blinding, on large sample size at 1 or 3 centre's are recommended to prove significant safety and efficacy of these drugs.

**Conflict of interest:** None declared

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