ORIGINAL RESEARCH PAPER

Gynecology

KEY WORDS: Infertility, anovulation, conception, Unani medicine, meta analysis.

# EFFECT OF UNANI FORMULATIONS IN ANOVULATORY INFERTILITY: A META - ANALYSIS

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ABSTRACT

**Introduction:** Anovulation is one of the major cause of female infertility affecting 30% of couples and most women with anovulatory infertility have polycystic ovarian syndrome. 10-15% of couples have difficulty in conception and many will seek specialist fertility care atleast once during their reproductive life time. In classical Unani text, anovulation (*Toole ehtebase mani)* is mainly caused by abnormal cold temperament. Hence, defect in ovaries leads to faulty production of ovum, which is either due to *qillate maddae manwia* or *fasade mani.* The aim of this paper is to evaluate the potent Unani formulation in anovulatory infertility via meta-analysis.

**Methods:** The inclusion criteria of anovulatory infertility considered were anovulation, menstrual irregularities, polycystic ovarian disease and normal seminogram. Systematic review and meta analysis of existing randomized controlled studies was done. All data used were abstracted from previously published studies. Relevance was initially evaluated via titles and then determined from abstracts. Outcome measures were ovulation and conception.

**Result:** Poly herbal Unani formulations were found to be more effective in achieving conception, whereas other Unani formulations were comparable in inducing ovulation.

**Conclusion:** Poly herbal Unani formulation is considered better in treating patients with anovulatory infertility to increase the conception rate.

## INTRODUCTION:

Infertility affects 10-20% of couples[1] and 40% of infertility cases are due to female factors and ovulatory dysfunction accounts for 30% of it.[2,3,4] The causes of anovulation include hypothalamic failure, hyperprolactinemia, polycystic ovarian syndrome, premature ovarian failure, subclinical hypothyroidism, adrenal failure and obesity. Out of these disorders, polycystic ovarian syndrome is the commonest, easily diagnosed and most treatable cause of an anovulatory infertility[5] 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 a greater risk for the development of endometrial cancer. [6,7] In most women with ovulatory dysfunction, ovarian stimulation is the primary treatment and fertility drugs are often used to induce ovulation.[8] Ovulation-inducting agent have their own specific adverse effects such as ovarian hyperstimulation syndrome (OHSS), miscarriages, multiple births, and birth defects[1]; for this reason, more couples are seeking towards alternative medicine, especially herbal medicine.

Unani system of medicine (USM) has a holistic approach towards the treatment and prevention of disease. *Al Majoosi* quoted the concept of ovulation as "an ovary produces a follicle which secretes ovum, the later reaches the uterine cavity through the fallopian tubes".[9] *Toole ehtebase mani* (anovulation) is caused mainly by *sue mizaj barid* which solidifies the ovum leading to anovulatory infertility.[10,11] Any sort of defect in ovaries leads to faulty production of ovum, which is either due to oligo-ovulation/anovulation or dysovulation.[12] *Baroodat* causes obstruction in the flow of ovum and menstrual blood towards the uterus.[9] It solidifies the ovum [10,13] 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 [7] or excessive intake of cold items in diet.[10] Various formulations has been mentioned in classical Unani literature for anovulatory infertility possessing the properties like *muqawwi rehm* (uterine tonics), *moaene hamal* (helpful in conception) *and moallide mani* (ovulation inducing) which has to be used from 5th day of menstrual cycle (corresponds to ovulation inducing drugs) [9,10] This shows that the concept of ovulation induction was well known to Unani physicians. Clinical trials have confirmed the positive effect of USM in treating infertile women with ovulatory dysfunction. The aim of present meta-analysis was to evaluate the potent Unani formulations to improve fertility among infertile women with anovulation.

## METHODS:

Sources: PubMed, Ovid, and Cochrane Library databases were searched using the key words infertility, anovulation, ovulatory dysfunction, ovulation induction, clomiphene citrate, complementary therapy, alternative medicine, herbal medicine, Unani medicine, randomized controlled trial etc.

**STUDY SELECTION:** Criteria for inclusion and exclusion of studies were established prior to the literature search. Inclusion criteria of anovulatory infertility considered were women of reproductive age with infertility and anovulation, menstrual irregularities, polycystic ovarian disease and normal seminogram. Studies were excluded if they were not randomized, not providing information related to ovulation and pregnancy rates, animal trials, missing data, not clearly identify the herbs used, duplicate publications of other studies previously identified. Systematic review and meta analysis of existing randomized controlled studies (RCTs) was done and all data used were abstracted from previously published studies. Relevance was initially evaluated via titles and then determined from abstracts. Articles were retrieved from databases by electronic search. Only articles that satisfied the selection criteria were included in meta-analysis. Approval from institutional review board is not required to conduct the meta analysis of previously published studies. RCTs using Unani medicine as intervention, clinical studies conducted in India and reported in the English language were included in the study selection.

**TYPES OF PARTICIPANTS:** Female patients in reproductive age group with anovulatory infertility were included in the study; tubal disease and unexplained infertility were excluded. Anovulation was diagnosed clinically with symptoms & confirmed with investigations (TVS reveals no evidence of ovulation and serum progesterone levels that fell below the normal values during the mid-luteal phase).

**TYPES OF INTERVENTIONS:** Experimental interventions encompassed Unani medicine, like in Kafeel *et al* study,[14] polyherbal Unani formulation {*Withania somnifera* (*Asgand*), *Anogeissus latifolia* (*Gule Dhawa*), *Nymphaea alba* (*Gule Nilofar*) and *Barleria prionitis* (*Piyabansa*) }was used as test drug as it is beneficial in anovulatory infertility.[12,15,16] All ingredients were taken

in equal quantity and grinded to make fine powder, 6 g was administered orally with milk twice daily for 5 days (from $D_5$ of cycle) [10,15,16] for 3 cycles. In Majeedi *et al* study[17], single drug *Asparagus recemosus* (*Satavar*) was used as test drug as it contains phytohormones (steroidal saponins & glycosides) which stimulates ovulation;[18] 6 g powder of satavar was administered orally [16,19] with milk twice daily from $D_{1-14}$ of cycle for 3 cycles. Control interventions comprised of conventional medicine (clomiphene citrate 50 mg once daily for 5 days). No adverse effects were identified from the studies included in this review.

**DATA EXTRACTION:** Primary outcome was ovulation and secondary outcome was conception. The process of data abstraction examined the methodological characteristics of each study and treatments received with particular regard to note the type, doses, mode and duration of treatment.

Data Analysis: After compilation into 2x2 table form for each study, data were analyzed and presented as odds ratio with 95% confidence interval was used as a valid way of describing an intervention effect. Differences were considered statistically significant when p-value was < 0.05. In particular, Odds ratio describes the multiplication of the odds of the outcome that occur with use of the intervention. Chi Square test was used for analysis of data. Forest plot was created using MedCalc-statistical soft ware for meta- analysis of proportions.

## RESULTS:

**STUDY DESCRIPTION:** Two studies were included in the final analysis. The included studies [14,17] reported data on 70 infertile women (30 and 40 in Kafeel *et al* & Majeedi *et al* studies respectively). A total of 6 cycles were analyzed (3 in each study).

**TABLE NO.1: Effect of Unani Formulations on Ovulation**

| Cycle | Study | Events (%) | Total | OR | 95% CI | P value |
|---|---|---|---|---|---|---|
| 1st | Majeedi *et al* | 5 (25) | 20 (100) | 0.5 | 0.12-1.93 | 0.31 |
| | Kafeel *et al* | 8 (40) | 20 (100) | | | |
| 2nd | Majeedi *et al* | 6 (30) | 20 (100) | 1.000 | 0.25-3.86 | 1.000 |
| | Kafeel *et al* | 6 (30) | 20 (100) | | | |
| 3rd | Majeedi *et al* | 6 (30) | 20 (100) | 0.35 | 0.09-1.28 | 0.11 |
| | Kafeel *et al* | 11(55) | 20 (100) | | | |

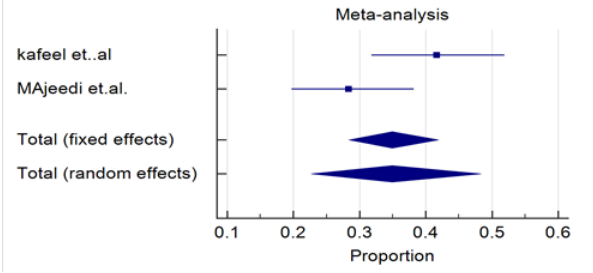


**FIG NO-1: Forest plot showing proportion of ovulation in studies**

**TABLE NO.2: Effect of Unani Formulations on Conception**

| Cycle | Study | Events (%) | Total | OR | 95% CI | P value |
|---|---|---|---|---|---|---|
| 1st | Majeedi et al | 0 | 20 (100) | 0.18 | 0.00-4.00 | 0.27 |
| | Kafeel et al | 2 (10) | 20 (100) | | | |
| 2nd | Majeedi et al | 0 | 20 (100) | 1.000 | 0.01-52.8 | 1.000 |
| | Kafeel et al | 0 | 20 (100) | | | |
| 3rd | Majeedi et al | 0 | 20 (100) | 0.12 | 0.00-2.52 | 0.17 |
| | Kafeel et al | 3(15) | 20 (100) | | | |

**OR-Odds Ratio, CI- Confidence Interval, $X^2$ test**

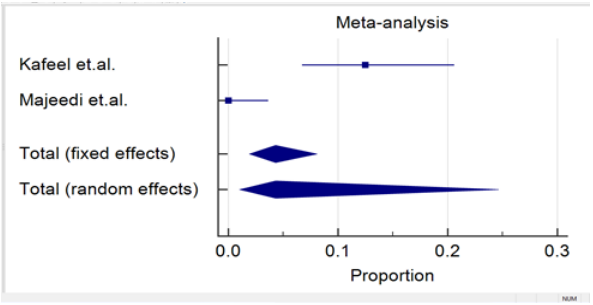


**FIG NO-2: Forest plot showing proportion of conception in studies**

## DISCUSSION:

After combining the data from included studies, ovulation rate was equivalent in both the studies, conception rate was better in Kafeel et al[14] study (as 5 patients got conceived in 1st and 3rd cycle respectively) then Majeedi et al[17] study; though the effect was not significant statistically. This shows that Poly herbal Unani formulations were found to be effective in achieving conception, whereas other Unani formulations were comparable in inducing ovulation. The weakness of this analysis was publication bias was not tested in consideration of the low power due to small number of studies included and intervention effect is likely to reduce due to small sample size (< 100 participants).

## CONCLUSION:

The current meta-analysis demonstrated that Poly herbal Unani formulation is better in treating patients with anovulatory infertility which helps in conception probably by correcting the cause of anovulatory infertility. Presence of multiple active compounds in them provide a potentiating effect such as they enhance the immunity of the body, regularize the menstrual cycle and induce the ovulation by maintaining hormonal balance due to the presence of phytohormones.[20] However, owing to few published studies investigated, further, well designed, adequately powered multicentric RCTs are needed before evidence-based recommendation can be provided regarding the effectiveness of Poly herbal Unani formulation in the management of anovulatory infertility.

**CONFLICT OF INTEREST:** None declared, no funding from any source.

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