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Original Research Article

## Effectiveness of folic acid in unexplained infertility

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### ABSTRACT

**Background:** Folic acid is commonly used by infertile women worldwide. However, studies on the effect of folic acid in women with unexplained infertility are lacking. This aim of this study was to evaluate the effectiveness of folic acid in women with unexplained infertility.

**Methods:** This prospective multicentric study was performed from June 2019 to July 2020 in women with unexplained infertility attending the fertility clinic. In this study, 50 women with unexplained infertility who satisfied the inclusion and exclusion criteria were started on folic acid therapy. The effectiveness of therapy was evaluated on the basis of successful conception and adverse effects if any.

**Results:** Folic acid therapy showed a marked improvement in infertility status measured in terms of successful conception. After initial 12 weeks therapy successful conception was achieved in 40 (80%) women without any adverse effects.

**Conclusions:** Folic acid supplementation has a positive effect on pregnancy outcome in women with unexplained infertility without any adverse effects. Folic acid is thus a safe and cost-effective option in women with unexplained infertility.

**Keywords:** Conception, Folic acid, Infertility

### INTRODUCTION

One in ten couples worldwide has been affected by infertility and has caused severe stress in marital life.<sup>1,2</sup> The standard infertility treatment in form of Assisted Reproductive techniques adds to this stress and economic burden on the affected couples.<sup>3</sup> In about 20% of couples the exact cause of infertility is unknown and are diagnosed as couples with unexplained infertility.<sup>4</sup>

Folic acid, one of the B complex vitamins, has been associated with infertility in a positive manner.<sup>5</sup> Folic acid plays an important role in oocyte quality and maturation along with improved implantation and normal continuation of pregnancy.<sup>6</sup> Folic acid has an important role in DNA synthesis, epigenetic modification and cell proliferation.

Folic acid deficiency affects especially proliferative cells like neural tube cells in the fetus, thus increasing the risk of neural tube defects in particular.<sup>7-10</sup> Factors associated with folic acid deficiency are nutritional deficiency, malabsorption and may be associated with hyperhomocysteinemia.<sup>2</sup> Pre-conceptual folic acid therapy increases folic acid concentration and decreases resultant homocysteine concentration in follicular fluid.<sup>11</sup> This adds to improved quality of embryo and thus chances of successful conception. In addition, a study of women taking multivitamins containing folic acid showed a reduced risk of ovulatory infertility.<sup>12</sup> Folic acid therapy in women with unexplained infertility and pregnancy outcome has not been studied extensively. Women with unexplained infertility do not normally receive a proper diagnosis as a result of the fact that a uniform definition is lacking.<sup>13</sup> Such women might also be sub-fertile rather than infertile.

The aim of this study was to study the effectiveness of folic acid therapy in women with unexplained infertility and successful conception. This will enable better understanding of the role of folic acid in unexplained infertility.

## METHODS

The prospective multicentric observational study was conducted at infertility clinic/family OPD at 171 MH, INHS Asvini and INHS Sandhani from June 2019 to July 2020.

### Inclusion criteria

Women with unexplained infertility only were included in the present study.

### Exclusion criteria

Patients with other causes of infertility such as tubal factor, male factor were excluded from the study.

In this study, 50 women with unexplained infertility who satisfied the inclusion and exclusion criteria were started on Folic acid therapy. They were started on folic acid as per the standard protocol using 5 mg tablet once a day. Successful conception is confirmed by a positive urine pregnancy test and clinically by intrauterine gestational sac observed on USG corresponding to 6 -7 weeks of pregnancy.

In a previous study, intake of folic acid at 250 mcg/day for 4 weeks was shown to decrease plasma homocysteine concentrations significantly and to increase mean plasma folate concentrations to 22.5 nmol/l.<sup>14</sup> Therefore, this plasma folate cut-off value was used to define folic acid supplement use: women with plasma folate concentrations of 22.5 nmol/l were defined as folic acid supplement users and women with plasma folate concentrations <22.5 nmol/l were defined as nonusers. For assessment of pregnancy outcome in relation to folate status, women with unexplained infertility were divided into two groups according to plasma folate concentration: 22.5 nmol/l and <22.5 nmol/l.

### Statistical analysis

The statistical analysis of the data thus collected is done by observational method of data analysis and computed in results respectively.

## RESULTS

Of the 50 women with unexplained infertility 45 (90%) cases were with primary infertility and 5 (10%) cases with secondary infertility.

**Table 1: Demographic characteristics.**

Variable	Range	Mean
Age (years)	20-30	26
Duration of infertility (years)	2-5	2
Primary infertility no. (%)	45 (90)	54
Secondary infertility no. (%)	5 (10)	

As shown in Table 1 the mean age of women with unexplained infertility was 25 years. The mean duration of infertility 2 years.

### Major outcomes of the study

Major outcomes of this study are shown in Table 2. After the initial 12-week folic acid therapy successful conception was achieved in 40 (80%) of women. The remaining 10 cases are on regular folic acid therapy.

**Table 2: Major outcomes of the study.**

Outcomes	Number (%)
Successful conception	40 (80)
Spontaneous conception	35 (70)
Ovulation induction	5 (10)

This finding is significant and in line with the research conducted by Boxmeer et al.<sup>15</sup>

Folic acid therapy is effective in achieving successful conception in women with unexplained infertility.

### Successful conception

Successful conception was achieved in 40 (80%) patients as shown in Table 3.

**Table 3: Successful conception.**

Successful conception	Number (%)
Spontaneous	35 (70)
Ovulation induction	5 (10)
Total	40 (80)

Out of the 40 patients with successful conception, 35 conceived spontaneously and rest with standard ovulation induction protocol as shown in Table 3.

This result is comparable to the research conducted by where successful conception rate was observed in 73% of women with unexplained infertility.<sup>16</sup>

### Safety profile

No any major adverse effect was noted during the therapy. This enabled a better compliance of the patient for the 12-week folic acid therapy in this study.

## DISCUSSION

This study showed that in women with unexplained infertility folic acid therapy has a positive impact on achieving a successful conception.

A majority (80%) of women with unexplained infertility in the present study achieved successful conception which is comparable to other studies as shown in results and is supported by the research conducted by McGuire et al.<sup>17</sup> Study conducted by Baraka et al and Timmermans et al showed that higher educational level and age also improves the folic acid intake in women with unexplained infertility. Other factors associated with increased intake of folic acid supplements are higher age. Even in the present study, the mean age of women with unexplained infertility was higher i.e., 26 years.

The studies conducted by De wallet, Zestra et al throw light on the use of folic acid, which is strongly linked to pregnancy and prevention of neural tube defects.<sup>18,19</sup> All this factors along with the cost effectiveness of folic acid enhances the compliance to folic acid therapy Lane.<sup>20</sup>

The recent studies have shown that folic acid therapy increases serum folate concentrations more than dietary folate, as folic acid has overall stable chemical structure and better bioavailability than naturally occurring folates (Elkin and McNulty).<sup>21,22</sup> Also Homocysteine concentration is inversely correlated to the folate concentration in blood was found by study of Scott et al.<sup>23</sup>

Till date, studies on folic acid supplement and pregnancy outcome in women with unexplained infertility are lacking. In the present study, the study group was well defined, as only women with unexplained infertility were included which adds to the strength of this study.

## CONCLUSION

This study shows the effectiveness of folic acid therapy in women with unexplained infertility by achieving successful conception with no any major adverse effects. Folic acid therapy is a cost effective and safe option in unexplained infertility.

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