

Induction of Ovulation in Primary Infertility: A Prospective Study

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ABSTRACT

Background: Until the middle of last century, infertility was only a diagnosis with a very little or no hope of treatment. This study was done to compare the ovulation rate and pregnancy rate between patients treated with clomiphene citrate alone and those treated with clomiphene citrate along with single dose of urinary FSH (uFSH) (75 IU).

Methods: A prospective, randomized study was carried out on 50 patient of primary infertility attending Department of Obs. and Gynae, NIMS. Medical College, Jaipur from January 2017 to September 2017. Patients were allocated to two groups at random. Group A: Patients in this group were administered clomiphene citrate in a dose 50-100 mg per day from days 3-7 of menstrual cycle. Group B: Were given clomiphene citrate 50-100 mg. per day from days 3-7 of menstrual cycle along with single dose of urinary FSH (uFSH) 75 IU on 3rd day of menstrual cycle. The cases were simultaneously monitored by Ultrasonography, Basal Body Temperature (BBT) record and cervical mucus study.

Results: The single dose of Urinary FSH (uFSH) on 3rd day when used with clomiphene citrate from 3rd to 7th day menstrual cycle is better regimen for ovulation induction as well as for conception as compared to clomiphene citrate alone. This combination is simple to use and cheap. The risk of ovarian hyperstimulation syndrome (OHSS) is avoided

because of controlled ovarian stimulation. This exogenously administered FSH compensates adverse effects of clomiphene citrate induced increase in LH and this FSH also promotes good follicular growth and recruitment hence the chances of ovulation as well as conception is increased. More and more estradiol is also generated within the growing follicles which provides favorable uterine environment to fertilized ovum.

Conclusion: The single dose of Urinary FSH (uFSH) on 3rd day when used with clomiphene citrate from 3rd to 7th day menstrual cycle is better regimen for ovulation induction as well as for conception as compared to clomiphene citrate alone.

Keywords: Clomiphene Citrate, Ovulation, Primary Infertility.

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INTRODUCTION

Although population explosion has become a national problem, yet many marriages have resulted in childlessness. The problem of Barren marriage led the Greeks & Romansto the altars of Deemester and Ceres, Hindus to the temples of Lord Amar-Nath and Lord Jagan-Nath in the Past, while the present trend is to visit the infertility clinic.¹

Involuntary infertility is a world-wide problem but its frequency varies from area to area. A very few studies have been made to assess the problem of infertility. W.H.O. (1975) has reported that about 5 per cent of the couples are involuntarily infertile. The problem of infertility is more pronounced in Africa. Studies had estimated that approximately one out of seven marriages was involuntarily childless. Recent studies indicate that infertility affects approximately 10 per cent of couples.^{2,4}

With the recent inauguration of a nation-wide campaign to prevent polio, all are intimately aware of the steps being taken in the field of preventative medicine to eliminate communicable disease.

Although infertility affects roughly 10% of the married population, a figure much larger than that for poliomyelitis, nevertheless, except for the introduction of antibiotics in the early 30's in Germany for the prevention and against the spread of pelvic infections, little thought or study has gone into prophylaxis against infertility. A review of the last four annual meetings of the American Society for the Study of Sterility reveals only one paper that is directed towards the prevention of future infertility in the young unmarried woman.^{5,6}

Until the middle of last century, infertility was only a diagnosis with a very little or no hope of treatment. The knowledge of physiological mechanisms governing the reproduction was incomplete and the therapeutic armamentarium was inadequate. After years of diligent work medical team has been successful to find tools for infertility which has proven a boon for infertile women.⁷ Various attempts have been made to induce ovulation. These methods are: Medical Methods and Surgical Methods.

Medical methods includes drugs used in induction of ovulation which has following categories: (a) Stimulation of ovulation (Clomiphene citrate, Letrozole, HMG, FSH) (b) By reduction of raised levels of Androgen (Dexamethasone), Prolactin (Bromocriptine) and Insulin (Metformin), (c) Substitution Therapy for hypothyroidism (Thyroxin), Diabetes mellitus (Antidiabetic drugs).⁸ This study is done to compare the ovulation rate and pregnancy rate between patients treated with clomiphene citrate alone and those treated with clomiphene citrate along with single dose of urinary FSH (uFSH) (75 IU).

MATERIALS AND METHODS

A prospective, randomized study was carried out on 50 patient of primary infertility attending Department of Obs. and Gynae, NIMS Medical College, Jaipur from January 2017 to September 2017. In all patients history was taken especially menstrual and obstetrical history. Detailed physical examination and all preoperative investigations were done.

Inclusion Criteria

1. Anovulatory women.
2. Age less than 35 years
3. Euthyroid patients
4. Normo-prolactinaemic patients

Exclusion Criteria

1. Male factor for infertility
2. Tubal factor for infertility
3. Uterine factor for infertility
4. Cervical factor for infertility
5. Pelvic or other factor for infertility

Patients were allocated to two groups at random:

Group A: Patients in this group were administered clomiphene citrate in a dose 50-100 mg per day from days 3-7 of menstrual cycle.

Group B: Will be given clomiphene citrate 50-100 mg per day from days 3-7 of menstrual cycle along with single dose of urinary FSH (uFSH) 75 IU on 3rd day of menstrual cycle.

USG was done by full bladder technique. Maximum follicular diameter was measured transversely, longitudinally and sagittally. The mean diameter is taken as the follicular size. Besides measurement of growing follicles, demonstration of early ovulatory changes of the follicle was considered.

- Disappearance with undistinguishable corpus luteum.
- Collapse with gradual replacement of a cystic corpus luteum.
- Irregular cyst gradually decreasing in size.
- Invasion of solid echoes. "filling in" of echogenic area without decrease in size.
- Free fluid in cul-de-sac demonstrated in the USG by Irregular cystic structure in the Base of uterus.
- Sign of high endometrial proliferation SO called "Ring sign" Instead of a line.

The cases were simultaneously monitored by Basal Body Temperature (BBT) record and cervical mucus study.

The patients were provided with BBT thermometer and chart. They were advised to measure the oral temperature every morning for 2 minutes before rising and a record was kept.

For cervical mucus study parameters - the amount, spinnbarkeit (Threadability) crystallization capacity (ferning) of mucus were noted. For cervical mucus study before performing digital examination a clean dry Speculum was inserted into the vagina and the cervix was exposed. A swab stick was then inserted into cervical canal (approximately up to internal os) rotated clockwise three times and slowly withdrawn. On withdrawal of the swab stick the amount of mucus obtained was noted. A drop of mucus placed on slide and coverslip applied on the slide then the coverslip withdrawn. This indicates the stretchibility of the mucus (spinnbarkeit).

Thus the response of drug given to patients was assessed between 12-18 days of menstrual cycle by following method.

- a. Basal body temperature (BBT)
- b. Cervical mucus study.
- c. Endometrial thickness measured by ultrasonography.
- d. Follicular monitoring with Transvaginal ultrasonography (TVS).

Table 1: Demographic division on the basis of age.

Age	Group-A		Group-B		Total
	n	%	n	%	
15-25 yrs.	20	80%	22	88%	42
25-35yrs.	5	20%	3	12%	8
Total	25		25		50

Table 2: Distribution of cases according to socio-economic status (ICMR Classification).

Group	Income per month	Patients	
		n	%
I	1000 and above	5	10%
II	500-999	20	40%
III	200-499	20	40%
IV	Below 200	3	6%
V	Below 100	2	4%

Figure 1: Rural / Urban Distribution of cases.

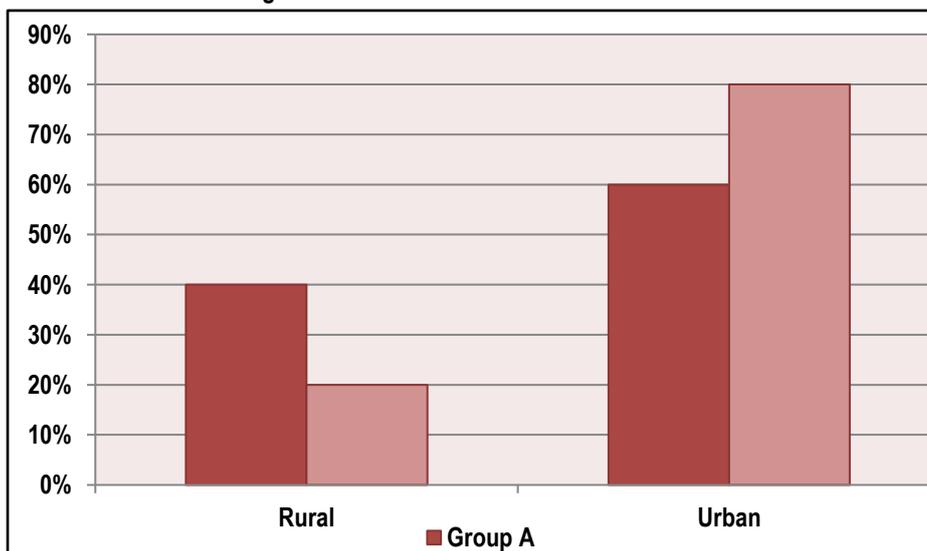


Figure 2: Distribution of cases according to literary status.

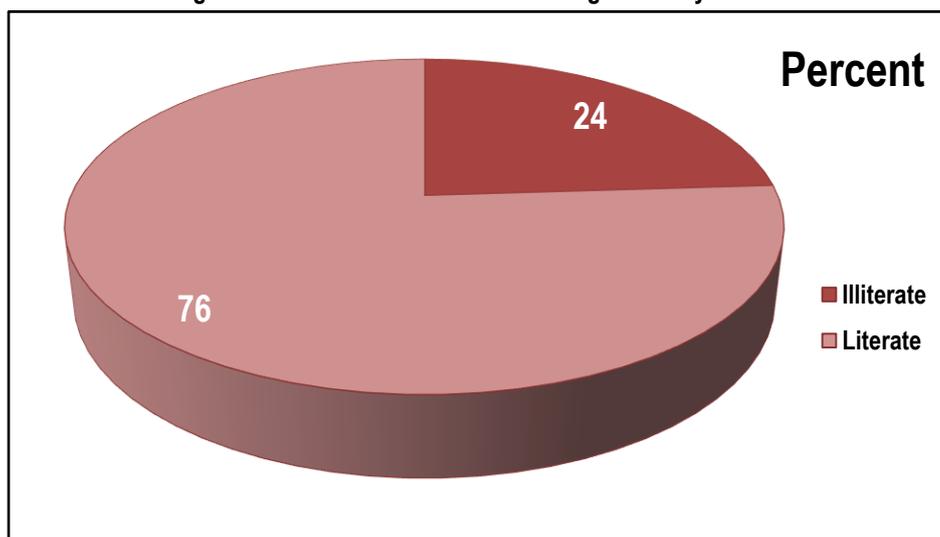


Table 3: Distribution of cases according to duration of marriage.

Duration of marriage	Group-A		Group-B		Total
	N	%	N	%	
1-5 yrs.	13	52%	20	80%	33
6-10 yrs.	10	40%	3	12%	13
11-15 yrs.	1	4%	2	8%	3
16-20 yrs.	1	4%	0	0%	1
>20 yrs.	0	0%	0	0%	0
Total	25		25		50

Table 4: Distribution of cases according to associated complaints.

According complaints	Group -A		Group-B		Total
	N	%	N	%	
Pain abdomen	20	80%	22	88%	42
White Discharge	2	8%	3	12%	51
Backache	1	4%	0	0%	1
Galactorrhea	1	4%	0	0%	1
Vague pain	1	4%	0	0%	1
Total	25		25		50

Table 5: Distribution of cases according to menstrual history.

Menstrual history	Group A		Group B		Total
	N	%	N	%	
Regular menstruation	20	80%	23	92%	43
Amenorrhea	0	0%	0	0%	0
Oligomenorrhea	4	16%	2	8%	6
Hypomenorrhea	0	0%	0	0%	0
Polymenorrhea	0	0%	0	0%	0
Dysmenorrhea	1	4%	0	0%	1

RESULTS

Table 1 shows majority of patients are in age group 15-25 years. 20 patients (80%) in group A belong to 15-25 years while only 5 patients (20%) are of 25-35 years age. 22 patients (88%) in group B belong to 15-25 year while only 3 patients (12%) belong to 25-35 years. In group A 2 patients were below 19 years of age as early marriage is common in Indian Subcontinent. Both of these women were illiterate. The difference in age between group A & B is not significant ($P > 0.05$). As shown in Figure 1, 15 patients (60%) in group-A came from urban area. 10 patients in group-A were from rural area. Majority of group-B patients 20 patients (80%) were from urban area Only 5 patients (20%) in group – B were from rural area. Number of patients attending infertility clinics is derived maximally from urban areas. The difference in two groups in relation with residence is not significant ($P > 0.05$).

Table 2 enlightens that about 40 patients (80%) of the group belong to group-II and III according to ICMR classification having income in the range of 200-999 Rs. per month. About 38 patients (76%) were educated. Only 12 patients (24%) were uneducated. This higher percentage of female literacy is because of the reason that majority of the patients in this study belonged to urban area [Figure 2]. As shown in table 3 that majority of patients in both groups, 13 patients (52%) in group-A and 20 patients (80%) in group-B were married for 5 yrs. of age. 10 patients (40%) in group A were married for 6-10 years, Only 1 patients was married 11-15 years Back, similarly only 1 patient was married 20 years Back in group A. These 2 patients gave history of consulting some Quacks, Ayurvedic and homeopathic doctors with no results, and then attended the hospital. Similarly in group B only 3 patients (12%) were married 6 - 10 years Back and 2 patients (8%) were married 11-15 years back. The difference in Duration of marriage between group A & B is not significant ($P > 0.05$). Pain abdomen was a major associated complaint in 20 patients (80%) of group A and 22 (88%) in group-B. The difference in associated complaints is both groups A and B is not significant ($P > 0.05$) [Table 4]. Patients attending hospital for treatment of infertility were having normal menstruation in flow, duration and frequency (Table-5). Only in 4 patients (16%) of group-A and 2 patients (8%) in group-B were having oligomenorrhea. Only 1 patient in group A was having painful periods. The difference in Menstrual history between group A and B is not significant ($P > 0.05$). 25 patients in group A were given clomiphene citrate alone. 13 patients (52%) out of total 25 ovulated. 25 patients in group B were given clomiphene citrate along with single dose Urinary FSH (uFSH) 75 IU im on 3rd day of menstrual cycle. 20 patients (80%) out of total 25 patients ovulated. The difference in ovulatory response to stimulation in both groups was statistically significant ($P < 0.05$), i.e. group B superior to group A for ovulation inductor [Table 6].

4 patients (16%) in group A and 3 patients (12%) in group B showed evidence of luteinized unruptured follicle (LUF) in USG. The difference in group A and B in relation to LUF is not significant ($P > 0.05$). 8 patients (32%) in group A were resistant of clomiphene citrate. They didn't ovulated even when clomiphene citrate was given upto 150 mg dose for a maximum of 3-4 cycles. Only 2 patients (8%) in group B were resistant to treatment. The difference in Resistance to drugs between groups A & B is statistically significant ($P < 0.05$), i.e. more patients were resistant when clomiphene alone was used while good results are obtained in clomiphene resistant cases when gonadotropins are used along with clomiphene. 13 patients (52%) got the honour of being mother when given a combination of clomiphene with uFSH 75 IU single dose on 3rd day of menstrual cycle. The results were comparatively poor when only clomiphene citrate was used. Only 6 patients (24%) in group A were able to conceive. The difference in conception rate between group A and B is statistically significant ($P < 0.05$) proving group B superior to group A [Table 7]. All patients undergoing treatment for ovulation were instructed to maintain their BBT chart. 13 patients (52%) in group A showed Biphasic BBT chart i.e. rise in BBT after ovulation. 20 patients (80%) in group B showed Biphasic BBT charting. Only 12 patients (48%) in group A and 5 patients (20%) in group B showed monophasic BBT chart. The difference in BBT pattern in Both group A and B is statistically significant ($P < 0.05$) [Table 8]. Stretchibility of cervical mucus was found to be more in group B than in group A. The range of spinnbarkeit was higher in group B 7-10 cm while in group A only 0-3 cm was noted. The standard error of difference in mean of spinnbarkeit between group A & B is statistically significant ($P < 0.05$) [Table 9]. Moreover the decrease in stretchibility of cervical mucus in group A was noted on 15th day while in group B it was noted on 14th day predicting the day of ovulation to be 13th day in group B and 14th day in group A. Endometrial thickness was found to be more in group B in range of 10-12 mm, while in group A comparatively thinner endometrium was found. The standard error of difference in mean of endometrium thickness between group A and B is statistically significant ($P < 0.05$). Moreover the increase in endometrial thickness on 15th day in group A and on 14th day in group B predicts the day of ovulation to be 14th day of menstrual cycle in group A and 13th day in group B, early ovulation in group B [Table 10]. Table 11 enlightens that average size of follicle in group A in range of 16-18 mm while in group B big follicle of about 24 mm size was noted. The difference in follicular size between group A and B is significant. In group A follicle ruptured on day 14 while comparatively early ovulation was noticed on day 13 in group B. None of the patients showed any signs of hyperstimulation syndrome because of regular follow up and investigation by USG.

Table 6: Distribution of cases according to response to stimulation.

Group	Stimulation	Ovulation		L U F (Luteinized unruptured follicle)		Resistant	
		N	%	N	%	N	%
A	25	13	52%	4	16%	8	32%
B	25	20	80%	3	12%	2	8%
Total	50	33		7		10	

Table 7: Distribution of cases according to conception rate.

Group	Stimulation		Conception	
	N	%	N	%
A	25		6	24%
B	25		13	52%

Table 8: Distribution of cases in correlation to BBT and ovulation.

	Group A		Group B		Total
	N	%	N	%	
Biphasic	13	52%	20	80%	33
Monophasic	12	48%	5	20%	17
Total	25		25		50

Table 9: Comparative study of cervical mucus (spinnbarkeit)

Day of Menstrual cycle	Spinnbarkeit (cm)			
	Group A (mean value)		Group B (mean value)	
12 th day	3		10	
13 th day	3		10	
14 th day	3		9	
15 th day	1		8	
16 th day	1		8	

Table 10: Comparative study of endometrial thickness

Day of Menstrual Cycle	Endometrial thickness (mm)	
	Group A (mean value)	Group B (mean value)
12 th day	4	10
13 th day	4	10
14 th day	4	11
15 th day	5	12
16 th day	6	12
17 th day	7	12
18 th day	7	12

Table 11: Comparative study of follicle size (mm)

Day of Menstrual Cycle	Group A(size of follicle)	Group B(size of follicle)
12 th day	16 mm	24 mm
13 th day	18 mm	Rupture
14 th day	Rupture	-
15 th day	-	-
16 th day	-	-
17 th day	-	-
18 th day	-	-

DISCUSSION

In women who do not respond to standard clomiphene citrate regimens, combination regimens have been proposed. Clomiphene citrate has been used in combination with insulin-sensitizing agents (eg, metformin), glucocorticoids, exogenous gonadotropins, and IUI.⁹⁻¹¹

Bypassing the cervix, IUI combined with clomiphene citrate is thought to increase pregnancy rates in women with unexplained infertility and surgically corrected endometriosis, perhaps by correcting undetected defects in ovulatory or sperm transport mechanisms and increasing the density of motile sperm available to released eggs. The routine use of IUI to improve pregnancy rates in women receiving clomiphene citrate has not been completely studied. However, investigations by Legro RS¹² suggest that the use of IUI may improve per-cycle pregnancy rates in patients even when semen parameters are normal. Although no studies directly compare clomiphene citrate alone with clomiphene citrate and IUI, combined retrospective analysis of studies by Coutifaris C¹³ estimates a 5.6% cycle fecundity with clomiphene citrate alone compared to 8.3% when combined with IUI. Clomiphene citrate combined with glucocorticoids has been shown to induce ovulation in women who fail clomiphene citrate alone. In a RCT by Guzick DS¹⁴ women with clomiphene citrate-resistant PCOS and normal dehydroepiandrosterone sulfate levels had a significantly higher rate of ovulation when dexamethasone was added, compared with the clomiphene-citrate plus placebo group (75% vs 15%, $P < .001$).

Downs KA et al¹⁵ obtained baseline serum estradiol level and then administer gonadotropins. A serum samples for estradiol was obtained each day. If the serum estradiol level didn't double after 3-5 days the dose of gonadotropins were increased by factor of 50%. This technique of 50% increase in daily dose of gonadotropins at specific interval was continued until estradiol level became at least twice the baseline concentration.

They claimed that higher pregnancy rate can be achieved if USG is combined with estrogen monitoring. The guiding principle has been to administer HCG when mature follicles correlate with an estrogen level of 200-400 pg per mature follicle (>13 mm).

Serum Hormone assay using Radio immunoassay (RIA) techniques being expensive has not been included in my study which might be a cause of less good results. One of the most important criteria for the selection of patients for clomiphene therapy is pretreatment evaluation of patients regarding FSH levels. Patients with FSH > 40 mIU/ml usually don't respond to therapy with clomiphene because of either absent or resistant ovarian follicles.

Glazener CM¹⁶, achieved very high ovulation rate and conception rate of 86% and 42% using clomiphene. All patients in their study were evaluated for baseline FSH levels considering the fact that increased level of FSH indicates impending ovarian failure; those patients were excluded from the study. Radio Immunoassay (RIA) methods for serum FSH assay are very expensive hence in my study baseline FSH assay is not done in routine; hence some patients, who failed to ovulate with clomiphene may be because of subtle elevation in level of serum FSH which went undiagnosed.

One Important fact was also revealed during my study. All those patients who ovulated in group A and B were of age group 15-25 year. The decline in fertility among married couples with advancing age has been repeatedly documented. In a study of

almost 3000 donor insemination cycles in one center, the cumulative conception rates after 3,6 and 12 cycles were 21% 40% and 62% for patients less than 30 years old, compared with 17% 26% and 44% for women 30 years and older.

This age related decline in fertility can be explained on the basis of fact that the follicular loss begins when the total number of follicles reaches approximately 25000, a number reached in normal women at age 37-38. This loss correlated with a subtle but real increase in FSH and decrease in inhibin. These changes reflect the reduced quality and capability of aging follicles.

The changes in the later reproduction years reflects either lesser follicular competence as the better primordial follicles respond early in life, leaving the lesser follicles for later or the fact that the total follicular pool is reduced in number. There is high incidence of abnormal responses in women age 35 and 85% women with increased FSH level respond poorly to ovarian stimulation.

Clomiphene citrate has got antiestrogenic effect on cervical mucus which may cause discrepancy between ovulation and conception. In my study only 24% patients conceived with clomiphene. The results don't correlate with the results of Wu CH¹⁷. They achieved 30% pregnancy rate with clomiphene. 15 patients in their study were treated with 100 ug ethinyl estradiol from days 10 to 14. Out of these 15 patients; 2 became pregnant. Hence the ethinyl estradiol given exogenously can improve cervical mucus in clomiphene treated patient, thus one can achieve high pregnancy rate. Clomiphene citrate by virtue of its action at the hypothalamic level increases GnRH secretion. GnRH stimulates production of both FSH & LH by pituitary. While FSH promotes follicular recruitment and growth with intra-follicular oestrogen production in early follicular phase, elevated level of LH may antagonize these beneficial effects on FSH. Advantages of adding an ampoule of Urinary FSH (uFSH) along with clomiphene citrate are – 1. Addition of one or two more follicles in the cohort. 2. Adverse effect of clomiphene citrate induced LH is compensated by addition of exogenous FSH. 3. More oestradiol is generated within developing follicle. 4. Therefore chances of effective ovulation & pregnancy are enhanced. 5. Treatment is simple & cheap. 6. There is no risk of ovarian hyperstimulation syndrome (OHSS) because of controlled and guided ovarian stimulation.¹⁸⁻²⁰

In this study single dose of urinary gonadotropin was used which produced controlled ovarian stimulation hence risk of developing ectopic pregnancy is minimized; however preconception counseling of all patients in study group with regards to tubal pregnancy and its consequences was done.

CONCLUSION

To conclude single dose of Urinary FSH (uFSH) on 3rd day when used with clomiphene citrate from 3rd to 7th day menstrual cycle is better regimen for ovulation induction as well as for conception as compared to clomiphene citrate alone. This combination is simple to use and cheap. The risk of ovarian hyperstimulation syndrome (OHSS) is avoided because of controlled ovarian stimulation. This exogenously administered FSH compensates adverse effects of clomiphene citrate induced increase in LH and this FSH also promotes good follicular growth and recruitment hence the chances of ovulation as well as conception is increased. More and more estradiol is also generated within the growing follicles which provides favorable uterine environment to fertilized ovum.

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