

Research Article

Agnucaston and Clomiphen Citrate in Infertile Patients with Polycystic Ovaries

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Abstract

Objectives: To study the effect of agnucaston with clomiphen citrate in infertile patients with polycystic ovaries.

Study type: Controlled trial.

Materials and Methods: One hundred infertile cases with polycystic ovaries randomized into two groups fifty (50) cases received clomiphen citrate 50 mg from second day of menstruation two tablets per day for 5 days in addition with agnucaston (agnus castus, Binoreca) two tablets per day from the first day of menstruation for 14 days the other group received only clomiphen citrate 50 mg two tablets per day from second day for 5 days.

Results: Group 1 (combined agnucaston with clomiphen citrate the pregnancy rate is 30 out of 50 (60%) while the second group the (clomiphen only group) pregnancy rate is 15 out of 50 (30%).

Keywords: Agnucaston; Clomiphen citrate; Infertility; Polycystic ovaries

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, with a prevalence of up to 10%. Various diagnostic criteria have been proposed, generally centered on the features of hyperandrogenism and/or hyperandrogenemia, oligo-ovulation and polycystic ovarian morphology [1]. Despite being heterogeneous in nature, the hallmarks of the disease are hyperandrogenism and chronic anovulation. Since its description in 1935 by Stein and Leventha [2,3]. Much has been learned about the pathophysiology of PCOS from its neuroendocrine underpinnings to an ever-growing understanding of the link between obesity, Insulin Resistance (IR) and PCOS [4]. Chronic anovulation often presents as oligomenorrhea, amenorrhea, dysfunctional uterine bleeding, and/or infertility. Interestingly, however, around 20% of patients with PCOS may describe normal menstrual cycle [5]. When clinically evaluating a patient for the possibility of PCOS, it is also important to search for signs of IR. Upper-body obesity is a key component of the IR syndrome [6]. However, obesity is not required for the diagnosis of PCOS with perhaps only 35% to 50% of these patients being obese [7-10].

The number of follicles and ovary volume are both important in the ultrasound evaluation. The criteria for PCOS put forth by Adams et al. are the most often cited: the presence of ≥ 10 cysts measuring 2–8 mm around a dense core of stroma or scattered within an increased amount of stroma [11]. A recent proposal to modify these criteria has been put forth by Jonard et al., [12] “increased ovarian area (>5.5 cm²) or volume (>11 mL) and/or presence of ≥ 12 follicles measuring 2 to 9 mm in diameter (mean of both ovaries)” [13]. These criteria had a specificity of 99% and a sensitivity of 75% for the diagnosis of PCOS. If the ovarian morphology is normal, then biochemical testing is undertaken. If any one or more of the following are noted, the diagnosis is confirmed: elevated LH, fasting glucose/insulin <4.5 , and/or elevated testosterone or free androgen index (in the absence of late-onset congenital adrenal hyperplasia [14].

Agnucaston

Composition

Each film-coated tablet 120.5 mg contains: Active Ingredient Dry extract of the fruit of the chaste tree extract.....20 mg Excipients.

Povidone, lactose 1 H₂O, magnesium stearate, macrogol, tacl, ammonium methacrylate copolymer, titanium (IV) oxide (E171), yellow iron oxide (E172), indigone lacquer (E132).

1 film-coated tablet contains: 4.0 mg dry extract of chaste tree fruits (Special extract BNO 1095) (7-11:1); extracting agent: ethanol 70 % (v/v) other ingredients: Lactose-monohydrate 25.0 mg.

Pharmacological action

Pharmacological investigations suggest that aqueous alcoholic Agnus castus extracts exerts their effects via a dopaminergic principle of action thereby inhibiting prolactin release.

Bicyclic diterpenes have been shown to contribute to the dopaminergic effects of Agnus castus extract BNO 1095. These substances bind to the human dopamine receptor subtype 2 and dose-dependently lower the prolactin release in cultured rat pituitary cells. Several clinical investigations show that administration of Agnus castus extract to women displaying latent hyperprolactinemia or increased prolactin resulted in a reduction of prolactin levels.

The prolactin-suppressive effect of Agnucaston has shown to be an effective treatment for PMS (premenstrual syndrome) and associated symptoms.

Indications

For the treatment of premenstrual syndrome and associated symptoms such as breast tenderness and mood changes.

Contra-indications

- In case of known allergy against chaste tree fruit or any other

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component of the medicine

- In case of pituitary tumors
- In case of mastocarcinoma.

Warnings

A regulation of the menstrual cycle also increases the probability of becoming pregnant. Patients with the rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Agnucaston® Film-Coated Tablets.

Materials and Methods

Objectives

To study the effect of addition of agnucaston with clomiphen citrate in infertile patients with polycystic ovaries.

Study title

Agnucaston and clomiphen citrate in polycystic ovaries

Study duration

June 20 12 to June 2013

Study type

Randomized controlled trial

Study site

Benha university school of medicine obstetrics and gynecology department.

Ethical approval

The study approved by the scientific committee of the department.

Sample size

One hundred case (100).

Method of randomization

Serial number according to the order of examination and the first 50 cases take the agnucaston arm the next 50 takes only clomiphen citrate.

Exclusion criteria

Other causes of infertility (non PCOS).

Groups of the study

The patients divided into two groups according to the drugs of induction

(Group1) combined arm: Take agnucastone tab twice daily from the first day of menses for 14 days combined with clomiphen citrate tablet 50 mg two tablets per day from the second day of menstruation for five days.

(Group2) clomiphen arm: Take only clomiphen citrate 50 mg from day 2 of menses for 5 days two tablets per day.

Patient evaluation:

All patients subjected to the following:

History: personal, present, menstrual, and past history.

Examination: general, abdominal, and local examination.

Ultrasound folliculometry

From the seventh day of menses and then every other day till the follicles reached 20 mm.

Then human chorionic gonadotropin 1000 IU given intramuscular when follicles reached 20mm and the couple asked to have intercourse after 36hours then daily for 7 days with the following instructions:

No breast touch

No douching after intercourse except after 6h

Luteal support

With progesterone (prontogest) 400mg suppositories vaginally daily from ovulation day for 14 days with folic acid 2.5 mg

Pregnancy test

Quantitative HCG blood test done after 2 days missed period

Statistical analysis

Data analyzed by smith statistical packages (SSP)

Results

Results of this trial are tabulated in table 1 and table 2 and analysis in figure 1 and figure 2.

Groups	Group 1 (agnucaston+clomid)	Group 2 (clomid)
Total number	50	50
Pregnancy number	30(60%)	20(30%)

P value=0.0026 (highly significant)

Table 1: Pregnancy rate among studied groups.

Serial no	Age	BMI	Type of infertility	Duration of infertility	Hirsutism
1	20	25.2	primary	2	
2	22	26	primary	3	
3	30	28.5	secondary	5	
4	31	23	primary	7	hirsute
5	25	26.3	primary	3	
6	27	25.5	secondary	4	
7	28	30	primary	3	
8	30	25	primary	2	
9	33	24.2	secondary	4	
10	22	25.6	primary	3	
11	20	24	primary	4	
12	30	29.1	primary	5	
13	33	26.4	secondary	3	
14	25	25.2	primary	4	
15	27	23	primary	3	
16	26	24.3	primary	5	
17	22	24	primary	3	
18	23	26.7	primary	3	
19	22	23.3	primary	3	
20	25	24.8	primary	4	
21	29	26	primary	5	
22	28	25.1	secondary	3	

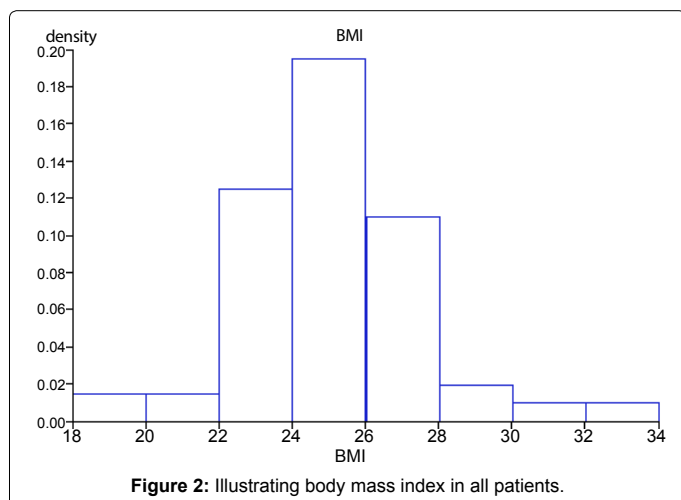
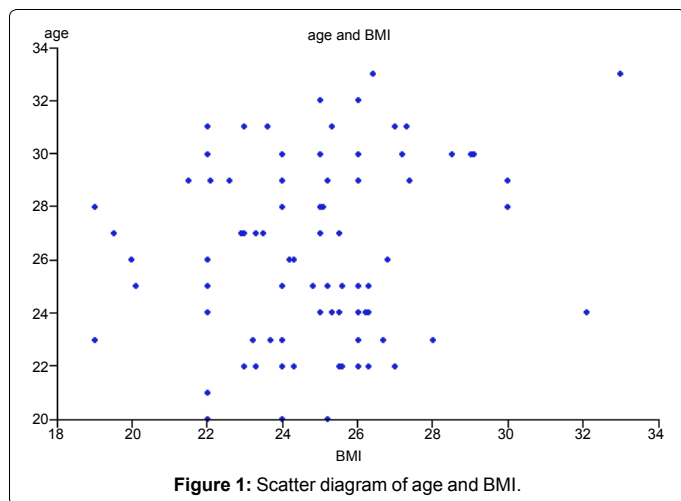
23	23	23.7	primary	6	
24	22	26.3	primary	3	
25	21	22	primary	2	
26	28	25	primary	4	
27	30	27.2	secondary	4	
28	31	22	primary	6	
29	22	23	primary	1	
30	26	24.2	primary	3	
31	25	24	primary	4	
32	24	26.3	primary	4	
33	26	22	primary	3	
34	27	23.5	secondary	5	
35	25	20.1	primary	2	
36	29	24	primary	4	
37	25	25.6	primary	5	
38	22	23	primary	2	
39	23	26	primary	2	
40	30	29	secondary	4	
41	31	27	secondary	3	
42	24	22	primary	3	
43	28	24	primary	3	hirsute
44	23	23.7	primary	2	
45	24	22	primary	2	
46	27	25	primary	4	
47	23	23.2	primary	2	
48	30	26	primary	5	
49	24	25.5	primary	3	
50	25	24	primary	3	
51	31	25.3	primary	5	
52	22	24	primary	2	
53	24	25	primary	2	
54	25	26.2	primary	3	
55	29	26	secondary	2	
56	25	27.4	primary	4	
57	24	32.1	primary	3	
58	23	28	primary	2	
59	23	24	primary	1	
60	25	22	primary	2	
61	30	25	secondary	4	
62	29	26	primary	4	
63	22	25.5	primary	2	
64	24	26	primary	3	
65	25	22	primary	3	
66	25	24	primary	3	
67	25	25	primary	3	
68	27	23.3	primary	4	

69	29	22.6	primary	4	
70	30	25	primary	5	
71	22	24	primary	2	
72	24	22	primary	2	
73	26	20	primary	3	
74	27	19.5	primary	3	
75	23	19	primary	3	
76	30	22	primary	6	
77	29	30	secondary	3	
78	20	22	primary	2	
79	22	24.3	primary	2	
80	27	22.9	primary	3	
81	29	24	primary	4	
82	24	25.3	primary	3	
83	26	24.2	secondary	3	
84	24	25	primary	3	
85	25	26	primary	4	
86	30	22	primary	4	
87	31	23.6	secondary	3	
88	32	25	primary	5	
89	23	26	primary	2	
90	28	24	primary	4	
91	29	25.2	primary	6	
92	29	22.1	primary	5	
93	28	19	primary	4	
94	29	21.5	primary	5	
95	30	24	secondary	4	
96	31	27.3	primary	6	
97	32	26	secondary	3	
98	22	27	primary	2	
99	25	24	primary	5	
100	26	26.8	primary	4	

Table 2: Clinical data of patients.

Discussion

Polycystic ovaries are a common disorder in infertile patients .many drugs used for induction of ovulation in combination with clomiphen citrate in polycystic ovaries. There is currently no ideal medical PCOS therapy that fully reverses underlying hormonal disturbances and treats all clinical features. Metformin has had an increasing role in PCOS management, improving clinical features (ovulation, cycle regulation, and potentially hirsutism) with positive cardiometabolic effects. It does not appear to induce weight loss, although based on studies in DM2 it may assist in preventing future weight gain. In infertility, the role of metformin remains controversial. It does reduce hyperstimulation in those on other fertility therapies; however more research here is important. When using metformin it is better tolerated if started at 500 mg of slow release daily and increased over weeks to months to reach 2 g daily. Lactic acidosis is a rare side effect in those with other significant illnesses including renal impairment. It is important to note that neither



metformin nor the OCP are approved by most regulatory authorities specifically for PCOS. About 30% of patients with polycystic ovaries have hyperprolactinemia therefore addition of anti hyperprolactinemic drugs in combination with clomiphene citrate may improve induction results and reduce also the miscarriage rate. Agnucaston (agnus castus) is an herbal compound with dopaminergic properties so reduce the level of prolactin and enhance the response of ovaries to stimulation by clomiphene citrate. The current work studied the effect of agnucaston in combination with clomiphene citrate in infertile patients with polycystic

ovaries and the results showed that addition of agnucaston doubled the pregnancy rate when given with clomiphene citrate. This work gives a hope for infertile patients before ICSI procedure as a final resolution with cost benefit.

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