

The Use of Diane – 35 in The Treatment of Infertility

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استعمال عقار دايان ٣٥ لعلاج العقم

الخلاصة :

، فترة العلاج امتدت من ٣-٦ اشهر حسب الاستجابة للعلاج .

أظهرت النتائج ان ٢٢٠ سيدة من بين ٥٨٩ حالة عقم اصبحن حوامل بينما ٣٦٩ لم يحملن ، من بين الحوامل ال ٢٢٠ كانت هناك ١٨٦ حالة عولجت بعقار دايان ٣٥ مع تحفيز المبيض بينما ٣٤ حالة حمل هن اللواتي عولجن بتحفيز المبيض فقط ، مما يعني ان تقريبا ٥٠ % من الحالات التي عولجت بعقار دايان ٣٥ مع تحفيز المبيض اصبحن حوامل بينما ١٤ % فقط من الحالات التي عولجت بتحفيز المبيض فقط اصبحن حوامل.

من خلال الدراسة ننصح بمناقشة أنواع العلاج مع السيدات ومن ضمنها نسب النجاح ، كلفة العلاج والاعراض الجانبية ، كذلك فان حالات العقم بسبب تكيس المبيض يمكن علاجها بشكل افضل باستعمال عقار دايان ٣٥ مع تحفيز المبيض .

دايان ٣٥ هو مركب هورموني من الاستروجين و البروجسترون مع مفعول مضاد للاندروجين يستعمل لعلاج حالات واعراض زيادة هورمون الذكورة لدى بعض السيدات مثل زيادة الشعر والزهيم ، كذلك له فائدة لعلاج بعض حالات العقم . أجريت دراسة حالات مسيطر عليها باستعمال دايان ٣٥ في علاج العقم عند السيدات اللواتي لديهن تكيس المبيض ، شملت الدراسة ٥٨٩ سيدة لديهن عقم مع تكيس المبيض تم اختيارهن من بين ٣٠٩١ حالة عقم لاسباب أخرى عدا تكيس المبيض ، السيدات راجعن مستشفى الديوانية التعليمي للنسائية والعيادات الخاصة في السماوة للفترة بين حزيران ٢٠٠٩ الى حزيران ٢٠١١ ، تم علاج ٣٧٢ سيدة بعلاج دايان ٣٥ مع تحفيز المبيض (التحفيز يتم باستعمال حب كلوميد و ابر كونال) بينما تم علاج ٢١٧ حالة بتحفيز المبيض فقط

Abstract :

Diane-35 is a hormonal compound of progesterone & oestrogen (with anti-androgen effect) used for the treatment of androgenic symptoms in females like severe cases of seborrhea & hirsutism , it can also be used for cases of infertility .

A case control study was performed about the use of Diane-35 in the treatment of infertility in women with polycystic ovarian syndrome , the study included 589

infertile ladies with polycystic ovary , they were chosen among 3091 infertile ladies for other different causes attending Al-Diwaniyah maternity hospital & a private clinic in Samawa city from June 2009 until June 2011 ..

372 women were treated with Diane-35plus induction of ovulation (inductionwithclomiphene + Gonal F) while 217 women were treated with

induction alone , duration of treatment was 3-6 months according to patient response, the results showed that 220 out of 589 became pregnant while 369 did not , among those 220 pregnant ladies 186 were those treated with Diane-35 plus ovulation induction while 34 were those treated with ovulation induction alone , this means that about 50% of ladies treated with Diane-35 plus induction became pregnant while only 14%

Introduction:

* Polycystic ovarian syndrome : it is the most common cause of anovulatory infertility , which is characterized by ovarian dysfunction , endocrinal problems , & hyper insulinemia , [1] . It occurs in 5 -10 % of females in reproductive age [2] . PCO is a heterogeneous condition which is defined by the presence of two out of three of the following criteria :

1. oligo and or anovulation
2. clinical and or biochemical hyper- androgenemia [2]
3. polycystic ovaries , which is referred to an ovary with 12 or more small follicles measuring 2-9 mm in diameter with increase in ovarian volume (more than 10 cm³) on transvaginal ultrasound [3] . The presence of single polycystic ovary rather than both ovaries is sufficient to provide the diagnosis [4] .

The pathophysiology of polycystic ovary syndrome is multifactorial and polygenic , about 50 % of first degree relatives have PCO suggesting a dominant mode of inheritance [5] .

of ladies treated with only ovulation induction became pregnant ..

We recommend that treatment modalities should be discussed with the patients including the success rates , cost , side effects , also cases of infertile polycystic ovaries that don't respond to ovulation induction alone are better treated with Diane-35 plus ovulation induction..

Commonly first degree male relatives appear more likely to have premature baldness & metabolic syndromes . [1]

*The pathophysiology of PCO :

There is hypersecretion of androgens by the stromal theca cells of the polycystic ovary which leads to the cardinal clinical manifestation of hyperandrogenism , as well as to a mechanism by which follicle growth is inhibited with the resultant excess of immature follicles [4] .

The hypersecretion of LH by the pituitary gland will stimulate testosterone secretion by the ovary , furthermore ; insulin is a potent stimulus for androgen secretion by the ovary and it amplifies the effect of LH , and additionally magnifies the degree of hyperandrogenemia by suppressing liver production of sex hormone binding globulin (SHBG) [6] .

The improvement in the lifestyle with the combination of exercise & well balanced diet (rich in vitamins & minerals but low in fats & carbohydrates) in order to achieve weight reduction is very important to improve the prospects of both spontaneous & drug induced ovulation in more than 80 % of

polycystic women , while pregnancy only occurs in about 40 % of them [7] .

*Diane – 35 :

It is a kind of oral contraceptive pills containing 2 mg of cyproterone acetate (which competes with DHT receptors , inhibits 5 alpha reductase activity , accelerates the clearance of testosterone , inhibits hypothalamic GnRH secretion in the frequency & amplitude so that the sum of all these effects will reduce the formation of ovarian sources of androgens & promote menstrual regularity) with 0.035 mg of ethinyl estradiol (a kind of estrogen) , it is widely used for the treatment of seborrhea & hirsutism in polycystic ovary women [8] .

Diane – 35 decreases LH production by the pituitary gland & subsequently androgen production through the inhibitory effect on the hypothalamus & the pituitary gland , after 3- 6 consecutive treatment cycles of Diane – 35 : the serum concentration of LH, testosterone & androstendione will return to the normal values , while SHBG increase significantly in PCO patients [8] .

Metformin is an insulin sensitizer by improving peripheral glucose uptake & utilize in a variety of ways

Materials & Methods:

A case control study performed in Diwanayah maternity hospital & private clinic in Samawa city during the period from June 2009 to June 2011, of 12760 attending the hospital & private clinic for different complaints ; 3091 women were complaining of infertility, of them 589 were cases of polycystic ovarian syndrome (they were labelled as such according to the criteria mentioned in the introduction).

in order to improve sugar metabolism & insulin sensitivity , thus indirectly reduce masculinizing hormone levels [9] .

Ovulation induction therapy in patients with PCO can be directed with pre – treatment period of 3 -6 months with Diane – 35 & metformin (850 mg twice daily or 500 mg three times daily) which directly reduce clomiphene citrate resistance or failure cases [9] .

*Management of PCO :

1. treatment of obesity by :
 - a. change of lifestyle
 - b. metformin therapy (insulin sensitizing agent)
 - c. bariatric surgery
 2. ovulation induction :
 - a. medical by :
 - I. clomiphene citrate
 - II. tamoxifen
 - III. gonadotrophins
 - IV. GnRH antagonist
 - V. Aromatase inhibitors (anastrosol)
 - b. surgical : laparoscopic ovarian drilling for patients with clomiphene citrate resistance or failure [10] .
- *long term consequences of PCO :
1. chronic hypertension
 2. type II diabetes
 3. cardiovascular disease
 4. breast cancer
 5. ovarian & endometrial cancer [1].

The plan of treatment was explained & discussed with the patients ; including the cost , the side effects , the possible success rate & accordingly the infertile women were grouped into 2 groups

- a.the group that was treated with Diane-35 & ovulation induction (using clomiphene citrate & Gonal-F) which were 372 women .
- B.the group that was treated with ovulation induction only which were 217 women .

Of those 372 women on mixed treatment (Diane + ovulation induction) 279 women were mild cases of polycystic ovary syndrome & were treated with Diane-35 for 3 months , while 93 women were moderate-severe cases of polycystic ovary syndrome & were treated with Diane-35 for 6 months , then ovulation was induced using

Clomiphene citrate & Gonadotropin-releasing hormone (GnRH) agonist for 6-

fertile	%	infertile	%	total	%
9669	75.77%	3091	24.23%	12760	100%

9 months in both groups .

The 217 women which were treated with ovulation induction alone using the same combination of drugs : the period of treatment was the same (6-9 months) .

Results :

Among 589 women with polycystic ovary syndrome ; 220 women got pregnant while 369 did not , of those 220 women who got pregnant ; 186 women were treated with a combination of Diane-35 & induction (mixed treatment) while 34 women were treated with induction of ovulation alone .

The 369 women who were not pregnant ; 186 of them were on mixed treatment while 183 of them were treated by induction alone .

The women whom treated with mixed treatment were 372 (279 of them were mild cases of PCO & 93 of them were moderate – severe cases of PCO),

Among 279 mild cases of PCO ; 150 women got pregnant while 129 did not , on the other hand among 93 women with moderate-severe cases of PCO ; only 36 of them got pregnant while 57 of them did not.

As a case control study: From 589 infertile women with PCOs, 220 got pregnancy and 369 did not. Both groups were asked for their past medical treatment. Of the pregnant: 186 were on mixed treatment and 34 were only on induction. The 369 who were not pregnant: 186 were on mixed treatment and 183 were only on induction.

Chi square = 3391.072

Df= 1

P value<0.01 which means highly significant difference

Pregnancy (conception):

	+	-	
mixed	186	186	372
induction	34	183	217
	220	369	589

Odd ratio= 6. 394

Chi square = 69.034

Df= 1

P value < 0.01

Yates Chi square = 67. 574

Yates P value < 0.01

For 279 milder forms:

A1	150	129	279
induction	34	183	217

Odd ratio=6.2

Chi square = 75.963

Df = 1

P value < 0.01

Yates Chi square = 74.289

Yates P value < 0.01

For 93 moderate to severe forms:

A2	36	57	93
induction	34	183	217

Odd ratio= 3.4

Chi square = 19.77

Df = 1

P value < 0.01

Yates Chi square = 18.747

Yates P value < 0.01

Conclusion :

1. About 25 % of all women attending Diwanayah maternity teaching hospital & Samawa private clinic at the time of study were complaining of infertility .
2. Cases of infertile polycystic women which were treated with a mixed regime of Diane – 35 & ovulation induction responded much better than those treated with ovulation induction alone (50 % of those treated with mixed regime got pregnant while only 14 % of women treated with ovulation induction alone got pregnant) .
3. Mild cases of PCO which were treated with mixed regime

responded much better than moderate-severe cases of PCO on the same treatment (55 % of mild cases of PCO got pregnant , but only 36 % of moderate- severe cases of PCO got pregnant) .

Recommendations :

1. We recommend that one has to discuss the medical treatment for infertility with all patients before starting it (we should discuss the cost , the side effects & success rate) .
2. Infertile PCO women who don't respond to ovulation induction alone are better treated by Diane-35 with ovulation induction.

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