Comparative studies on the therapeutic effect of low power laser bio-stimulation and clomid on the treatment of polycystic ovarian disease

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SUMMARY

Polycystic Ovary syndrome (PCOS) is the most common cause of anovulatory infertility. PCOS has been recognized as a disorder of ovulatory disturbance, hyperandrogenism, morphologic changes in the ovary, and insulin resistance. There are short and long term sequelae of PCOS. Short term sequelae are menstrual irregularities-including oligomenorrhea and amenorrhea, infertility, and hirsutism. Long term sequelae are diabetes due to insulin resistance and cardiovascular disease with abnormal lipid profile and endometrial hyperplasia. The corner stone in the management of PCOS are induction of ovulation and treatment of hirsutism. The available modalities for induction of ovulation are weight reduction, clomiphene citrate, insulin sensitizer as metformin, gonadotropin therapy and lastly by ovarian drilling using bipolar diathermy or laser. Despite these methods of treatment; still there are resistant cases for treatment, rising the need for a new modalities of treatment. Laser, using high power density, has been used for the management of ovarian disorders. This include laser drilling of PCOS with CO2 laser, Argon, KTP, and Nd:YAG laser with variable degrees of response. A 50 female Albino Wister rats weighting 180-200 gm were selected. They were divided into three groups: Group 1: Consists of 10 rats used as a control group. All animals received Femara (letrozole) 0.25mg daily for 20 days, Five rats were sacrificed at 21st day from the 1st day of Femara (letrozole) administration, and the remaining five at 24th day from the 1st day of letrozole administration. Group 2: Consists of 20 rats received 0.25 mg Femara (letrozole) daily for 20 days, then received clomiphene citrate (Clomid) 20 microgram daily for 2 days, then they were sacrificed at 24th day from the 1st day of letrozole administration. Group 3: Consists of 20 rats received 0.25 mg Femara (letrozole) daily for 20 days dissolved in CMC, At the 21st day animals received general anaesthesia where their abdomens were opened and their ovaries were exposed to Diode laser 150mj/cm2 using an apparatus - Intelite R 650-250 daily for 2 days exposure at the next day. All animals then sacrificed at the 24th day from the 1st day of Femara (letrozole) administration. Whole blood was collected for serum progesterone assay. Data were statistically described using Kruskal Wallis non parametric. Also ovaries were taken and processed for histopathological examination. Our study concluded that low power laser is a new, encouraging method for induction of ovulation. And it is more effective with less complication compared with clomid.
INTRODUCTION

Polycystic Ovary syndrome (PCOS) is the most common cause of anovulatory infertility. This syndrome was first described by Stein-Leventhal in 1934.

Recently, PCOS has been recognized not only as a disorder of ovulatory disturbance, hyperandrogenism, and morphologic changes in the ovary but also of insulin resistance (Hughes et al., 1990).

PCOS is found in about 50% of cases with anovulatory infertility, 87% of cases with oligomenorrhea, and 32% of cases with amenorrhea. There are short and long term sequelae of PCOS, (David, 2001).

Short term sequelae are menstrual irregularities-including oligomenorrhea and amenorrhea, infertility, and hirsutism. Long term sequelae are diabetes due to insulin resistance and cardiovascular disease with abnormal lipid profile and endometrial hyperplasia. Diagnosis of PCOS is based on major and minor criteria. Major criteria are, chronic anovulation, hyperandrogenism, and its clinical manifestations. Minor criteria are, insulin resistance, perimenarchal onset of hirsutism and obesity, elevated LH-to-FSH ratio, and intermittent anovulation (Hunag et al., 2007). The corner stone in the management of PCOS are induction of ovulation and treatment of hirsutism.

The available modalities for induction of ovulation are weight reduction, clomiphene citrate, insulin sensetizer as metformin, gonadotropin therapy and lastely by ovarian drilling using bipolar diathermy or laser, (William, 2001). Despite these methods of treatment; Still there are resistant cases for treatment, rising the need for a new modalities of treatment. Laser, using high power density, has been used for the management of ovarian disorders. This include laser drilling of PCOS with CO2 laser (Daniell, 1985), Argon (Keye and Dixon, 1983), KTP (Daniell and Tosh, 1986), and Nd:YAG laser with variable degrees of response. Recently, Al-Watban and Andres (2003) used He-Ne laser in ovarian biostimulation in chineneese hamster giving a dose of 60-600 mj/cm2 with average 180 mj/cm2 on three consecutive days, resulting in cell growth and proliferation.
Hot or high power laser is used mainly in surgical procedures and industries. Cold or low power laser has been used for healing of different tissues and enhancement of cellular proliferation as well as in physiotherapy. He-Ne laser is the most common type of laser used in medicine as a cold laser. PCOS can be induced in animals by chronic exposure to estrogen-given as subdermal implants, (McCarthy and Brawer, 2001), or through I/M injection of oily solution (Elisabet Stener-Victorin et al., 2003). Resulting in PCOS within 2 days and lasting more than 30 days. Also, PCOS can be induced in animals by aromatase inhibitor-Letrozole-in a dose of 0.1, 0.5 & 1 mg. P.Os for 21 days. Also keeping of high level of exogenous LH can stimulate and induce PCOS (Kafali et al, 2004). Treatment of PCOS in animals can be achieved by HMG injection with optimal dose of 15-20 IU FSH/LH once, (Ozgunen et al., 2001). Or by clomiphene citrate 100 μg/kg daily for 2 days or by letrozole 5 mg/kg daily for 2 days, (Kilic-Okman et al., 2003).

**Aim of the study :**

This study was designed and conducted to characterize and evaluate the effect of laser bio-stimulation on PCOS in experimental animals by different diagnostic tools.

**MATERIAL AND METHODS**

A 50 female Albino Wister rats weighting 180-200 gm were selected. They were divided into three groups:

**Group 1:** Consists of 10 rats used as a control group. All animals received Femara (letrozole) 0.25 mg daily for 20 days, (Kafali et al., 2004). Five rats were sacrificed at 21<sup>st</sup> day (1-A) from the 1<sup>ST</sup> day of Femara (letrozole) administration, and the remaining five at 24<sup>th</sup> day from the 1<sup>ST</sup> day of letrozole administration (1-B).

**Group 2:** Consists of 20 rats received 0.25 mg Femara (letrozole) daily for 20 days, then received clomiphene citrate (Clomid) 20 microgram daily for 2 days, then they were sacrificed at 24<sup>th</sup> day from the 1<sup>ST</sup> day of letrozole administration. Three rats in this group died and were excluded.

**Group 3:** Consists of 20 rats received 0.25 mg Femara (letrozole) daily for 20 days dissolved in CMC, At the 21<sup>ST</sup> day animals received general anaesthesia in the form of I/M injection of mixture of xylazine (12 mg/kg), and ketamine(8 mg/kg) where the abdomens were opened and their ovaries were exposed to Diode laser 150mj/cm2 using an apparatus - Intelite R 650-250 (Photo 1) - daily for 2 days. The power density was 30 mw / 0.2 cm2. The ab-
The domen was closed after burring the ovary under the skin to facilitate re-exposure at the next day. All animals then sacrificed at the 24th day from the 1st day of Femara (letrozole) administration. Six rats in this group died and were excluded.

**Histopathological examination:**

At the end of the study ovaries were taken and fixed in 10% buffered neutral formalin solution, processed by standard paraffin methods, sectioned at 4-5 μ, and finally stained with Hematoxylin and Eosin (Bancroft *et al.*, 1996). Whole blood was collected for serum progesterone assay, Data were statistically described using Kruskal Wallis non parametric analysis of variance (ANOVA) test. A probability value (p value) less than 0.05 was considered statistically significant.

Parametric data statistically analyzed by t-student test using SPSS computer program SPSS 14 (2006).

**RESULTS**

**Histopathological results:-**

Microscopic examination of ovaries from Group I (1-A), revealed follicular cysts that may reach up to 4 cysts / 1 microscopic field, (Fig. 1), together with severe congestion in most of the interstitial blood vessels (Fig. 2&3). Whereas in Group I (1-B), the follicular cysts were much more numerous than that of (1-A) nearly about 9 cysts / 1 microscopic field, (Figs. 4 & 5), With less severe congested blood vessels, (Fig. 6).

Histopathological examination of ovaries from Group II, showed 2 follicular cysts / 1 microscopic field in 40% of the examined ovaries, (Fig. 7), 3 follicular cysts / 1 microscopic field in 40% of the examined ovaries, (Fig. 8), and 5 follicular cysts / 1 microscopic field in the remaining 20% of the examined ovaries, (Fig. 9). Most of these cysts were accompanied with luteal cysts.

Pathological alterations of ovaries from Group III, revealed some follicular cysts, these cysts were accompanied with multiple luteal cysts, congestion, and slight interstitial tissues edema, and fibrous connective tissues proliferation (Figs. 10, 11 & 12).
Fig. (1): Ovaries of rats from **Group I control (A)** showing multiple follicular cysts (4 / microscopic field), (arrows). (H&E X 40).

Fig. (2): Ovaries of rats from **Group I control (A)** showing multiple follicular cysts (F), and congested vessels, (arrows). (H&E X 40).

Fig. (3): Ovaries of rats from **Group I control (A)** showing multiple follicular (arrows), and luteal cysts (L). (H&E X 40).
**Fig. (4):** Ovaries of rats from **Group I control (B)** showing several multiple follicular cysts (9/ microscopic field), (arrows). (H&E X 40).

**Fig. (5):** Ovaries of rats from **Group I control (B)** showing several multiple follicular cysts. (H&E X 40).

**Fig. (6):** Ovaries of rats from **Group I control (B)** showing slightly congested vessels, (arrows). (H&E X 40).
Fig. (7): Ovaries of rats from Group II showing (2 follicular cysts / microscopic field ) (arrows), and fibrous connective tissues proliferation (C), ( H&E X 40 ).

Fig. (8): Ovaries of rats from Group II showing (3 follicular cysts / microscopic field ) (F), and slight congestion (arrows), ( H&E X 40 ).

Fig. (9): Ovaries of rats from Group II showing (5 follicular cysts / microscopic field ) (F), and slight interstitial tissue edema (arrows), ( H&E X 40 ).
**Fig. (10):** Ovaries of rats from **Group III** showing (1 follicular cyst / microscopic field) (F), and multiple luteal cysts (arrows), (H&E X 40).

**Fig. (11):** Ovaries of rats from **Group III** showing (2 follicular cysts / microscopic field) (F), and multiple luteal cysts (arrows), (H&E X 40).

**Fig. (12):** Ovaries of rats from **Group III** showing (4 follicular cysts / microscopic field) (F), and severe congestion (arrows), (H&E X 40).
Hematological results
Table (1): Serum progesterone levels of the 3 studied groups of rats at the end of the treatment.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser Progesterone</td>
<td>14</td>
<td>1.2</td>
<td>21.1</td>
<td>9.09</td>
<td>4.41</td>
</tr>
<tr>
<td>Clomid</td>
<td>17</td>
<td>0.8</td>
<td>10.7</td>
<td>4.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>1.0</td>
<td>7.9</td>
<td>2.41</td>
<td>1.12</td>
</tr>
</tbody>
</table>

The cut off value of serum progesterone in ovulation is 3.6 ng/ml

Table (2): Ranks of serum progesterone following the treatment in each of the 3 studied group.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser Progesterone</td>
<td>14</td>
<td>27.07</td>
</tr>
<tr>
<td>Clomid</td>
<td>17</td>
<td>19.00</td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>15.90</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td></td>
</tr>
</tbody>
</table>

Statistical analysis of the hematological results:
Analysis of serum progesterone level in the 3 studied group

Table (3): Comparison between serum progesterone levels in control group with clomid treated group.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>Standard Error</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser Progesterone</td>
<td>20</td>
<td>2.41</td>
<td>0.25</td>
<td>2.977</td>
<td>0.041</td>
</tr>
<tr>
<td>Clomid</td>
<td>17</td>
<td>4.10</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The comparison indicating statistically significant difference at P <0.05.
Table (4): Comparison between serum progesterone levels in control group with laser treated group.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>Standard Error</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>20</td>
<td>2.41</td>
<td>0.25</td>
<td>5.54</td>
<td>0.000</td>
</tr>
<tr>
<td>Laser</td>
<td>14</td>
<td>9.09</td>
<td>1.17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The comparison indicating a statistically high significant difference (P < 0.001)

Table (5): Comparison between serum progesterone levels in clomid group with laser treated group.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>Standard Error</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomid</td>
<td>17</td>
<td>4.10</td>
<td>0.51</td>
<td>3.86</td>
<td>0.001</td>
</tr>
<tr>
<td>Laser</td>
<td>14</td>
<td>9.09</td>
<td>1.17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The comparison indicating a statistically significant difference (P < 0.001)

**DISCUSSION**

This study shows a significant ovulation rate following the use of low power laser ovarian biostimulation which is greater than the use of clomid (clomiphene citrate). The method that used to induce PCO in rats was the one reported by Kafali et al. (2004) in which aromatase inhibitor letrozole drug was used in a daily oral dose of 0.5 mg/kg body weight given orally for 20 days consecutively.

Letrozole is aromatase enzyme inhibitor. Aromatization is the reaction by which estrogens are synthetised from androgens. By blocking the aromatization step, the level of androgens increases while that of estrogens decreases. This elevation of androgens level imprint on the hypothalamus leading to a non cyclic release of gonadotrophins without peak of FSH or LH surge, resulting in arrest in ovarian follicles growth and maturation. Also excess androgens have direct suppressing effect on follicular growth and maturation (Speroff et al., 2004).
After successful induction of PCOS in rats, we investigated and compared the effect of clomiphene citrate, which is a well known drug that has always been used as a first line of treatment for induction of ovulation in the majority of cases of infertility due to anovulation, versus low power diode laser bio-stimulation for induction of ovulation. **Clomiphene citrate** (CC), a non-steroidal compound which has estrogen and antiestrogen effect, has a remarkable structural similarity to Estradiol (E2) which enables it to bind to E2 receptors in various tissues such as the hypothalamus, hypophysis, ovaries and the uterus and cervix. However unlike E2, CC is unable to induce the synthesis of new E2 receptors—a process essential for the continuous binding of E2 to the target cells as well as the expression of estrogenic action. The most commonly accepted simplistic view of CC action in the induction of ovulation is that it binds to the E2 receptors in the hypothalamus to create a state of hypoestrogenicity, thereby causing an enhanced gonadotrophin-releasing hormone (GnRH) release followed by an increased secretion of gonadotrophins which induces ovulation (**Burney et al., 2007**). The intrafollicular concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH), E2 and androgens contribute to follicular growth. CC is known to stimulate E2 synthesis in the ovaries which in turn stimulate formation of FSH and LH receptors in the granulosa cells of other small follicles which would not develop under normal circumstances and thus lead to development of additional follicles during the CC therapy. Thus CC may also act directly on the follicular apparatus to recruit additional follicles. Ovulation is known to occur in about 70% of cases treated by clomiphene citrate (**Speroff et al., 2004**). While pregnancy occurs only in about 25-30% of those cases. The low pregnancy rate is due to the anti-estrogenic effects of CC on the cervix, which would make it hostile to sperm penetration and on the endometrial growth which would therefore be un receptive to the embryo. Other reasons are premature luteinization, due to the advancement of the LH surge in some instances and the occurrence of un-ruptured follicles in others due to defective ovulatory mechanisms. CC may impair development of the granulosa cells and thus cause luteal phase defect. In this study the Diode laser at 650 nm wave length was used since its apparatus forms are small, portable, inexpensive, and can be modulated easily. Although it is not very well understood, many theories have been postulated about the mechanism of action for low level lasers. In the literature,
the three most often encountered theories are:

**Bioluminescence theory** - according to Russian researchers, DNA replication emits light at 630 nm. Since this is very close to the wavelength of the He-Ne and diode laser light, it is postulated that laser may accelerate DNA replication via photic stimulation. Laser irradiation at this frequency is said to be non mutagenic since it is not in the range to alter the genetic program by affecting chromosomal ultra structure.

The latter is more likely to occur at ultra-violet light irradiation at 300 to 400 nm.

**Cellular oscillation theory** - the laser beam carries electromagnetic oscillations of definite frequency. When it reaches the tissues the electromagnetic oscillations gradually "swing and excite" single cells. This is thought to eventually intensify the bionomical processes that ultimately regulate the performance of various vital organs.

**Biological field theory** - connections between tissues and organs in the intact organism are not limited to humoral effects and nervous control mechanisms alone. Rather, there exist unique around every cell, tissue and organ and higher structural levels (organism, organ) exerting a normalizing influence on lower levels (tissue cells). In polycystic ovarian disease, low power laser mostly produce its effect by inducing cell division and proliferation of granulosa cells which in turn can aromatize excess androgen produced by theca cells into estrogen. This change of the hormonal milieu from androgenic to estrogenic predominance enhances follicular growth and maturation. In laser treated group, six rats died, but only three from clomid treated group died. This can be explained by the fact that in laser group the abdomen of the rat was opened to expose the ovaries to direct laser beam. The abdomen was closed after laser application to be reopened on the second day to expose the ovaries to a second dose of laser. This might be the direct cause of increased mortalities in laser treated group. Regarding the histopathological findings, control letrozole treated rats group, showed polycystic ovary represented by: multiple follicles, theca cell proliferation, and arrested granulosa cells. The number of follicular cysts increased from 4 cysts/ 1 microscopic field immediately post letrozole treatment up to 9 cysts after 4 days. This observation denotes that within 4 days post letrozole treatment there was PCO changes, and any ovulation occurred at this period is related to the treatment received. Histopathological examination of the ovaries from rats received clomid
showed; multiple follicular cysts reaching 2 follicular cysts/l microscopic field in 40% of the examined ovaries, 3 follicular cysts/l microscopic field in 40% of the examined ovaries, and 5 follicular cysts/l microscopic field in 20% of the examined ovaries. This observation indicates that even with induction of ovulation by clomid there are still unresponsive follicles in most of the cases with corpus luteum present only in about 40% of the cases. Histopathological examination of ovaries from laser treated group showed; 1 follicular cyst/l microscopic field in 30% of the examined ovaries, 2 follicular cysts/l microscopic field in 50% of the examined ovaries, and 3 follicular cysts/l microscopic field in 20% of the examined ovaries. This result is less than that obtained in clomid treated group. In contrast to clomid treated group, most ovaries of this group contain multiple luteal cysts indicating ovulation in most animals of this group, better response and biostimulation to low power laser. On discussing the serum progesterone results, we can see that; the result of serum progesterone in control group does not reach the figure of cut off value that indicates ovulation except in three cases out of twenty. Spontaneous ovulation in PCO cases does not exceed 15% of the total number of the studied cases as shown in tables 1 & 2. Serum progesterone from clomid (clomiphene citrate) treated group indicated ovulation in 40% only. The maximum level of serum progesterone in this group reached 10 ng/ml with mean value 4ng/ml, While in laser treated group the figures are much higher. The maximum level of serum progesterone in laser group reaches 27 ng/ml, while the mean value reaches 8 ng/ml. Ovulation occurs in 70% of laser treated group. Comparison between serum progesterone level in control and clomid treated group, revealed that difference was statistically significant (P < 0.05). While comparing serum progesterone level in control and laser treated group, the difference was statistically highly significant (P < 0.001). On the other hand serum progesterone level in clomid with laser treated group resulted in difference which was statistically significant (P < 0.001).

Conclusion:

In conclusion low power laser is a new, encouraging method for induction of ovulation. As appeared in this study, it is more effective with less complication compared with clomid.

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دراسات مقارنة على التأثير العلاجي لأشعة الليزر والكلوميد في أمراض تكيس المبيض

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الملخص العربي

تشكل متلازمة تكيس المبيض أهم سبب في عدم التبويض مما يؤدي إلى فلة الخصوبة والاعقم. وكان أول من وصف هذه المتلازمة هما أشتيت ولفنتيل سنة 1934، وتتشمل هذه المتلازمة خلل في التبويض وارتفاع في نسبة هرمون الذكور ومعوية أكياس صغيرة في المبيض مع زيادة مقاومة الإستروجين ومتلازمة تقيس المبيض اثار على المدي القريب و البعيد منها: حدوث عقم، اضطراب في الدورة الشهرية و زيادة احتفال الاصابه بالسكر و قصور في شريان القلب و اضطراب نسبة الدهون في الدم، وتوجد عدة وسائل لعلاج تكيس المبيض منها نقص الوزن واستعمال الأدوية التي تزيد من هرمون الاستروجين (استعمال كلوميد و سترات الكلوميدين) و استعمال هرمون الجونادوتروبين وأخيرا العلاج الجراحي بكي المبيض.

و بالرغم من وجود هذه الوسائل المختلفه لعلاج تكيس المبيض إلا أنه توجد حالات لا تستجيب لهذه الوسائل مما يدعو الى البحث عن وسائل اخرى أكثر كفاءة، و الليزر هو نوع من اشعة الضوء لها طول موجي واحد و موحدة الاتجاه و متوازية. وقد
تم استعمال اللبزكر في علاج تكيس المبايض بالكلي عن طريق منظار البطن وقد لاحظ بعض الباحثين حدوث حث وزيادة انسجام في خلايا الجسم عند تعرضها الي لبزكر منخفض القوة مما دعا بعض الأطباء الي استعمالها خاصة في مجال العلاج الطبيعي والتآهيل.

ومن أنواع اللبزكر المشهورة في هذه الاستعمالات لبيض الهرمونات ولبزكر الدايوود. وقد تم اختيار ستين فارا (اثني) من فنّان التجارب لإجراء هذا البحث وقد تم اعطاءهم جميعاً مادة لبزكرول 50 مجم يومياً عن طريق الفم لمدة عشرين يوم متصلة، ثم تقسيمهم إلى ثلاث مجموعات.

المجموعة الأولى: تضم عشرين فاراً وتم ذبح عشرون منهم في اليوم التالي لانتهاء اللبزكرول والعشرة الباقين بعد أربعة أيام.

المجموعة الثانية: ضمت عشرين فاراً، تم حث التبويض فيهم عن طريق اعطاءهم مادة الكولوميد ( سترات الكولوميدين ) 20 مجم يومياً لمدة يومين متتاليين، ثم ذبحهم في اليوم الرابع والعشرين.

المجموعة الثالثة: تم تصور المبيض للبزكر دايوود 50 نانومتر 150 ملي جول 1 سم 2 لمدة يومين متتاليين.

تم اخذ دم الفنّان لقياس مستوي هرمون البروجسترون، وتم اخذ المبايض لفحصها باناثولوجيا لتحديد حدوث تبويض من عدمه وعدد البويضات ان امكن. وقد خلص البحث إلى النتائج التالية:

عقار اللبزكرول قادر على احداث تكيسات في مبيض الفنّان إذا تم اعطاؤه لمدة عشرين يوماً متصلة بجرعة 1 مجم / كجم. كل من عقار الكولوميد ولبزكر منخفض القوة تنتج عن استخدامهما حدوث تبويض، لكن كانت كفاءة التبويض بمعدلات أعلى وكثر كفاءة في مجموعات اللبزكر عنها في مجموعة الكولوميد.

المحمومون:

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أ. د. رؤى محمد غنام