Efficacy of Oral Micronized Progesterone when Applied via Vaginal Route

Roungsin Choavaratana MD*, Darapa Manoch MD*

* Department of Obstetrics and Gynaecology, Faculty of Medicine, Siriraj Hospital, Mahidol University

The aim of the study was to compare the efficacy of oral micronized progesterone when applied by the vaginal route. The comparative study of serum progesterone levels between oral and vaginal micronized progesterone administration was conducted in sixty female volunteers. The subjects were equally divided into two groups to receive the drug either via the oral or vaginal route. The subjects’ profiles showed that there was no significant difference in general characteristics between these two groups. The blood tests for estrogen and progesterone levels were performed on all volunteers before and after the drug administration. The data collected from the experiment revealed that the serum progesterone levels achieved by oral administration (5.06 ± 2.95 ng/ml) differed significantly (p < 0.001) from those achieved by vaginal administration (8.26 ± 4.09 ng/ml). The data also revealed that the serum progesterone levels of the oral administration group (4.23 ± 2.68 ng/ml) did not differ significantly (p = 0.925) from the other group (4.15 ± 3.40 ng/ml) when the serum estrogen level was less than 30 pg/ml. On the contrary, when the serum estrogen level was at least 30 pg/ml, there was a significant (p < 0.005) difference in the serum progesterone levels between these two groups (6.32 ± 2.99 ng/ml for the oral route and 9.76 ± 3.23 ng/ml for the vaginal route).

Results

The purpose of this study was to compare the efficacy of oral and vaginal micronized progesterone.

Material and Method

Sixty-post tubal sterilization women were enrolled in the study. They were divided into two groups equally. Both groups received micronized progesterone for one day only. The first group took two micronized progesterone capsules orally twice daily. The other group also took the same dosage but by the vaginal route. Blood sampling to examine progesterone and estrogen levels was done before the administration of micronized progesterone. Blood levels of estrogen and progesterone were detected again on the following day just after the last dose of the drug. Then, the serum progesterone levels collected from these two groups were compared in overall aspects, in the event that serum estrogen levels were less than 30 pg/ml and equal or greater than 30 pg/ml.

Correspondence to: Choavaratana R, Department of Obstetrics and Gynaecology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

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for the study. They were randomly divided into two
groups. Each group had thirty women. There was no
significant difference in the general characteristics of
the subjects in the two groups as shown in Table 1.

After the menstruation finished completely,
a blood test for estrogen and progesterone levels
was performed on all volunteers. Soon after that, they
all took micronized progesterone capsules by the
route of administration that had already been
randomly selected. On the following day, the blood
samplings were repeated again to examine any
change of both hormone levels. Changing patterns
of these hormones were summarized as shown in
Table 2. Both progesterone and estrogen levels of
the group that received micronized progesterone by the
vaginal route were significantly higher than in the
other group.

Regarding the estrogen levels, the volun-
teers were then divided into two groups. The first
group had an estrogen level of at least 30 pg/ml and
the other group had an estrogen level below 30 pg/ml.
The pattern of progesterone level was also altered as
shown in Table 3. When the estrogen level was lower
than 30 pg/ml, the blood level of progesterone admin-
istered orally did not significantly differ from the
group administered by the vaginal route. However,
when the estrogen level was at least 30 pg/ml, the
progesterone level was significantly higher in the
vaginal route of administration than in the oral
administration as shown in Table 3.

Discussion

Although corpus luteum deficiency is not
a common cause of infertility, its incidence was
found to be about 12.8% (4). However, it was believed
that the incidence may be higher when the assisted
reproduction technique was applied to the patient,
especially if GnRH agonist was used for ovarian
stimulation procedure (5-8). Therefore, in this circum-
stance, administration of progestrogen was neces-
sary. Nowadays, there are various progestrogen
preparations available in the market. The oral prepa-
rations are more commonly used than the injection form. This is probably due to patient compliance as oral administration is better. However, when micronized progesterone is taken orally, headache and dizziness are the common adverse effects. These adverse effects did not occur when the drug was administered via the vaginal route. Nevertheless, the efficacy between these two different routes of administration has to be considered.

Table 1. Patients general characteristics

<table>
<thead>
<tr>
<th></th>
<th>Oral route</th>
<th>Vaginal route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± SD)/years</td>
<td>32.22 ± 32</td>
<td>32.13 ± 32</td>
</tr>
<tr>
<td>Cycle length (Mean ± SD)/day</td>
<td>29 ± 3.24</td>
<td>29 ± 3.44</td>
</tr>
<tr>
<td>Weight (Mean ± SD)/kg</td>
<td>45 ± 4.33</td>
<td>45 ± 4.67</td>
</tr>
<tr>
<td>Height (Mean ± SD)/cm</td>
<td>148 ± 3.85</td>
<td>149 ± 2.21</td>
</tr>
</tbody>
</table>

Table 2. Progesterone and estrogen level after administration of micronized progesterone

<table>
<thead>
<tr>
<th>Routes of administration</th>
<th>Orally(n = 30)</th>
<th>Vaginally(n = 30)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in ΔP₄ level (Mean ± SD)</td>
<td>5.06 ± 2.95</td>
<td>8.26 ± 4.09</td>
<td>0.001</td>
</tr>
<tr>
<td>Level of E₂ (Mean ± SD)</td>
<td>29.14 ± 20.19</td>
<td>56.05 ± 38.38</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Unpaired student t-test, ΔP₄ = progesterone (ng/ml), E₂ = estrogen(pg/ml)

Table 3. Serum progesterone level in the event of two different estrogen levels, lower and equal or greater than 30 pg/ml

<table>
<thead>
<tr>
<th>Routes of administration</th>
<th>Orally</th>
<th>Vaginally</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase ΔP₄ level (Mean ± SD)</td>
<td>4.23 ± 2.68</td>
<td>4.15 ± 3.40</td>
<td>0.925</td>
</tr>
<tr>
<td>E₂ level &lt; 30 pg/ml</td>
<td>N = 18</td>
<td>N = 8</td>
<td></td>
</tr>
<tr>
<td>Increase ΔP₄ level (Mean ± SD)</td>
<td>6.32 ± 2.99</td>
<td>9.76 ± 3.23</td>
<td>0.005</td>
</tr>
<tr>
<td>E₂ level ≥ 30 pg/ml</td>
<td>N = 12</td>
<td>N = 22</td>
<td></td>
</tr>
</tbody>
</table>

* Unpaired Student t-test

Sixty volunteers were enrolled in this study. All were randomly divided into two equal groups. One group of thirty volunteers took micronized progesterone orally. The other group of thirty volunteers received the drug as a vaginal suppository. There was no difference in the general characteristics of these two groups (Table 1).

Vaginal mucosa is estrogen dependent tissue (9). As a result, it changes day by day as the level of estrogen swings during the menstruation cycle. This means that the vaginal mucosal maturity was also altered. Therefore, if estrogen is not properly produced in any cycle, the vaginal mucosa may be
poorly developed or become atrophied\(^{10}\). This could result in poor absorption of the drug when it is administered vaginally.

From the present study, the authors found that the serum progesterone level was significantly higher overall when micronized progesterone was administered vaginally than when it was administered orally (Table 2). However, the serum estrogen level of the vaginal administration group was also higher which may lead to more drug absorption. According to the data in Table 3, the women were separated into two groups according to the serum estrogen level. One group was composed of volunteers who had a serum estrogen level lower than 30 pg/ml. The other group had a serum estrogen level at least 30 pg/ml which is consistent with the early follicular development. The vaginal mucosa during this stage is also developing and starts to function cyclically. In the group that had the serum estrogen level less than 30 pg/ml, the serum progesterone level achieved from the oral route did not significantly differ from the vaginal route. It may be implied that even with poor development of vaginal mucosa, the absorption of micronized progesterone vaginal suppository is still as good as the oral administration. Furthermore, in the group with a serum estrogen level of at least 30 pg/ml, the serum progesterone level when micronized progesterone was administered vaginally was significantly higher than when the drug was administered orally. This result supports that the more maturity the vaginal mucosa achieves, the more absorption is yielded.

**Conclusion**

The authors conclude that the serum progesterone level achieved when micronized progesterone capsule was administered as a vaginal suppository is significantly higher than or at least the same as the level achieved by oral administration. In addition, if the serum estrogen level at that time is equal or greater than 30pg/ml, the serum progesterone level achieved by the vaginal route is significantly higher than that achieved by the oral route.

**Acknowledgement**

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**References**

ประสิทธิภาพของยาไมโครไนซ์โปรเจสเตอโรนชนิดกินเมื่อนำไปบริหารโดยวิธีการสอดทางช่องคลอด
เรืองศิลป์ เขาวัฒน์ ดาวรัตน์ มาโนช

การทดลองนี้มีจุดประสงค์เพื่อศึกษาประสิทธิภาพของยา micronized progesterone ชนิดกินเมื่อนำมาบริหารโดยการสอดทางช่องคลอด โดยศึกษาปรับที่ระยะดันโปรเจสเตอโรนในชีวิตระหว่างการรับยา micronized progesterone โดยการรับประทาน และการเหน็บช่องคลอดในอาสาสมัครเพศหญิงจำนวน 60 คน โดยแบ่งอาสาสมัครออกเป็น 2 กลุ่มเท่าๆกัน กลุ่มหนึ่งได้รับยาโดยการรับประทาน 三分之一กลุ่มนี้ได้รับยาโดยการเหน็บช่องคลอด จากข้อมูลของอาสาสมัครพบว่ากลุ่มนี้ทั้ง 2 กลุ่มนี้ไม่มีความแตกต่างกันอย่างมีนัยสำคัญ อาสาสมัครทุกคนจะถูกเจาะเลือดเพื่อวัดระดับโปรเจสเตอโรนและโปรเจสเตอโรนในชีวิตทั้งก่อนและหลังจากการหายข้อมูลที่ได้จากการทดลองแสดงให้เห็นว่าระดับโปรเจสเตอโรนในชีวิตรวมที่ได้จากการรับประทาน (5.06 ± 2.95 นาโนกรัม/มล.) แตกต่างอย่างมีนัยสำคัญ (p < 0.001) จากการสอดโปรเจสเตอโรนในชีวิตรวมที่ได้จากการเหน็บของช่องคลอด (8.26 ± 4.09 นาโนกรัม/มล.) นอกจากนี้ยังพบว่าเมื่อระดับเอสโตรเจนในชีวิตรวมอยู่ระหว่าง 30 พิโคกรัม/มล. ระดับโปรเจสเตอโรนในชีวิตรวมที่ได้จากการรับประทาน (4.23 ± 2.68 นาโนกรัม/มล.) ไม่แตกต่างอย่างมีนัยสำคัญ (p = 0.925) จากกลุ่มหนึ่ง (4.15 ± 3.40 นาโนกรัม/มล.) ในทางตรงกันข้าม เมื่อระดับเอสโตรเจนในชีวิตรวมอยู่ระหว่าง 30 พิโคกรัม/มล. กลับมีความแตกต่างอย่างมีนัยสำคัญ (p < 0.005) ระหว่างระดับโปรเจสเตอโรนในชีวิตรวมของกลุ่ม 2 กลุ่มนี้ (6.32 ± 2.99 นาโนกรัม/มล. สำหรับการให้ยาโดยการสอดทางช่องคลอด และ 9.76 ± 3.23 นาโนกรัม/มล. สำหรับการให้ยาโดยการเหน็บช่องคลอด)