Efficacy of Oral Micronized Progesterone when Applied via Vaginal Route

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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).

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Corpus luteum deficiency is defined as an inadequate progesterone production of the corpus luteum. Although the deficiency occurs uncommonly, its consequence can be an unsuccessful pregnancy[1-2]. Up until now various therapies have been developed to treat this inadequacy. Among these, proper ovarian stimulation is the most common one and has been used widely for a long time. However, in some circumstances, this deficiency still persists although the ovary was well stimulated. In such cases, direct supplementary of progestogen is required. Currently, progestogen is available in various preparations. Oral micronized progesterone is simple by means of its route of administration. However, some adverse effects have been reported when taking the progestrogen orally[3]. The common side effects were dizziness and some motion sickness. Such effects, on the contrary, were not found when the drug was administered via the vaginal route.

In addition to the assessment of its safety, it is also important to evaluate the efficacy of the drug. The purpose of this study was to compare the efficacy of oral and vaginal micronized progesterone.

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Material and Method

Sixty-post tubal sterillization 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.

Results

Sixty women who had no history of hypersensitivity to micronized progesterone volunteered

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 volunteers 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 administered 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.

Table 1. Patients general characteristics

	Oral route		Vaginal route	
Age (Mean SD)/years	32	2.21	32	3.13
Cycle length (Mean SD)/day	29	3.24	29	3 .44
Weight (Mean SD)/kg	45	4.33	45	4.67
Height (Mean SD)/cm	148	3.85	149	2.21

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

	Routes of administration				
	Orally(n = 30)		Vaginally(n = 30)		p value*
Increase in ΔP_4 level (Mean SD)	5.06	2.95	8.26	4.09	0.001
Level of E_2 (Mean SD)	29.14	20.19	56.05	38.38	0.001

* Unpaired student t-test, ΔP_4 = progesterone (ng/ml), E_2 = 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

	Routes of administration		
	Orally	Vaginally	p value*
Increase ΔP_4 level (Mean SD)	4.23 2.68	4.15 3.40	0.925
E2 level < 30 pg/ml	N = 18	N = 8	
Increase ΔP_4 level (Mean SD)	6.32 2.99	9.76 3.23	0.005
E2 level ≥ 30 pg/ml	N = 12	N = 22	

* Unpaired Student t-test

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 circumstance, administration of progestrogen was necessary. Nowadays, there are various progestrogen preparations available in the market. The oral preparation is 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.

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.

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ประสิทธิภาพของยาไมโครไนซ์โปรเจสเตอโรนชนิดกินเมื่อนำไปบริหารโดยวิธีการสอดทางช่องคลอด

เรืองศิลป์ เชาวรัตน์, ดาราภา มาโนช

การทดลองนี้มีจุดประสงค์เพื่อดูประสิทธิภาพของยา micronized progesterone ชนิดกินเมื่อนำมาบริหารโดยการสอดช่องคลอด ได้ศึกษาเปรียบเทียบระดับโปรเจสเตอโรนในซีรัมระหว่างการให้ยา micronized progesterone โดยการรับประทาน และการเหน็บช่องคลอดในอาสาสมัครเพศหญิงจำนวน 60 คน โดยแบ่งอาสาสมัครออกเป็น 2 กลุ่มเท่าๆ กัน กลุ่มหนึ่งได้รับยาโดยการรับประทาน ส่วนอีกกลุ่มหนึ่งได้รับยาโดยการเหน็บช่องคลอด จากข้อมูลของอาสาสมัครพบว่าลักษณะโดยทั่วไปของอาสาสมัครทั้ง 2 กลุ่มนี้ ไม่มีความแตกต่างกันอย่างมีนัยสำคัญ อาสาสมัครทุกคนจะถูกเจาะเลือดเพื่อวัดระดับเอสโตรเจนและโปรเจสเตอโรนในซีรัมทั้งก่อนและหลังการให้ยา ข้อมูลที่ได้จากการทดลองแสดงให้เห็นว่าระดับโปรเจสเตอโรนในซีรัมที่ได้จากการรับประทาน (5.06 $\pm$ 2.95 นาโนกรัม/มล.) แตกต่างอย่างมีนัยสำคัญ ($p < 0.001$) จากระดับโปรเจสเตอโรนในซีรัมที่ได้จากการเหน็บช่องคลอด (8.26 $\pm$ 4.09 นาโนกรัม/มล.) นอกจากนี้ยังพบว่าเมื่อระดับเอสโตรเจนในซีรัมน้อยกว่า 30 พิโคกรัม/มล. ระดับโปรเจสเตอโรนในซีรัมที่ได้จากการรับประทาน (4.23 $\pm$ 2.68 นาโนกรัม/มล.) ไม่ได้แตกต่างอย่างมีนัยสำคัญ ($p = 0.925$) จากอีกกลุ่มหนึ่ง (4.15 $\pm$ 3.40 นาโนกรัม/มล.) ในทางตรงกันข้าม เมื่อระดับเอสโตรเจนในซีรัมสูงอย่างน้อย 30 พิโคกรัม/มล. กลับมีความแตกต่างอย่างมีนัยสำคัญ ($p < 0.005$) ระหว่างระดับโปรเจสเตอโรนในซีรัมของผู้ป่วย 2 กลุ่มนี้ (6.32 $\pm$ 2.99 นาโนกรัม/มล. สำหรับการให้ยาโดยการรับประทาน และ 9.76 $\pm$ 3.23 นาโนกรัม/มล. สำหรับการให้ยาโดยการเหน็บช่องคลอด)