

Monitoring of ovulation induction with human menopausal gonadotropin and human chorionic gonadotropin by ultrasonography : prevention of ovarian hyperstimulation Syndrome

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ABSTRACT: We monitored follicular development by ultrasonography on 40 anovulatory women on the day when we switched from HMG to HCG, and measured the maximum follicular diameter (mFD) and the sum total of follicular cross sectional area (FA) and examined the correlations of both mFD and FA with ovulation or OHSS. The ovulatory rate with mFD of more than 18mm was 100%. The correlation coefficients between mFD and serum estradiol level and moreover, FA and estradiol level were 0.3817 and 0.8099, respectively. From the above results, it is concluded that in order to induce ovulation without the hazard of causing OHSS, it is best to switch from HMG to hCG when the patients have FA less than 7.0cm and mFD more than 18mm, respectively.

INTRODUCTION

HMG agent sometimes causes multiple pregnancy and ovarian hyperstimulation syndrome (OHSS) as its stimulation to the ovaries is strong. The proper preventative has not yet been established against multiple pregnancy, but as for the prevention of OHSS, at least, a rapid assay^{1, 2)} of estrogen in urine and serum to prevent the occurrence of severe OHSS has been developed. However, this method is not easy for clinical practice because it is time-consuming and complicated. The use of ultrasonography (USG) has spread lately and monitoring of follicular development with USG has been carried out extensively. However, the usefulness of USG as a method of prevention of side-effects from HMG-HCG therapy has not yet been examined sufficiently.

We monitored follicular development during

HMG-HCG therapy by USG and examined the relationship among maximum follicular diameter (mFD), total of cross sectional area of all follicles (FA) and OHSS. Moreover, we tried to establish the criteria for predicting the occurrence of side effects by USG.

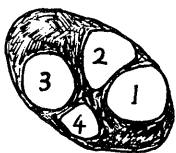
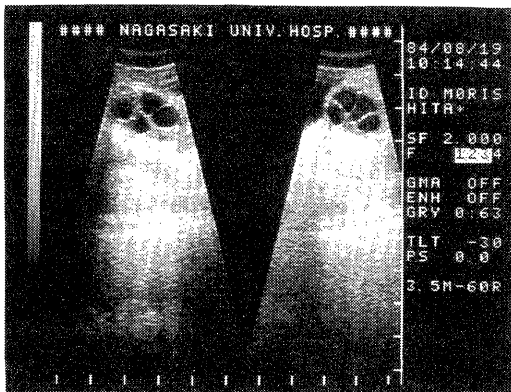
MATERIALS AND METHODS

We gave HMG-HCG therapy to 4 women with anovulatory cycles (12 cycles), 12 with 1st grade amenorrhea (26 cycles) and 24 with 2nd grade amenorrhea (50 cycles), total of 40 women (88 cycles). We gave 75–300 IU Pergonal^R (HMG) per day, 10 times as a rule, and on the next day 5,000 IU HCG, 1–3 times every other day. We started monitoring of the follicular development after we gave the 5th or 6th dose of HMG, using USG (Aloka Fansonic 190 sector scan) and measured the maximum follicular diameter (mFD) which was taken from both ovaries (when

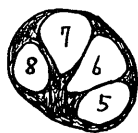
the follicle was elliptical, we measured the long axis), and the sum total of the cross sectional area of all follicles (FA) on an echogram including each largest follicle in the bilateral ovaries (Fig. 1).

Further, the cross sectional area of each follicle was measured by the formula for the elliptic area, $\pi ab/4$ (a: long axis, b: short axis). We practically calculated FA with a pocket computer. Also, we started gathering blood from the time FD became 12-13mm. After dividing it into serum and freezing it, we measured estradiol and progesterone en block by radioimmunoassay. Ovulation was judged by BBT, USG, progesterone and so on. We also examined the relation of mFD and FA with estradiol, as well as the relation between each parameter and ovulation or OHSS, and we tried to establish criteria for predicting the occurrence of side-effects by using USG.

The criteria for OHSS is established as fol-



right ovary



left ovary

Fig. 1. Follicular echogram of bilateral ovaries visualized in amenorrhic woman on HMG administration. The cross sectional area of all follicles in bilateral ovaries measured by the formula, $\pi ab/4$ (a: long axis, b: short axis), was 8.8cm.

lows: Moderate OHSS when the long axis of the ovary is more than 5cm, severe OHSS when it's more than 10cm, measured at the time when the ovary is most swollen, whether any other symptoms are present or not

RESULTS

1. The relation between the level of serum estradiol and ovulation or OHSS.

In 76 out of 88 cycles in which HMG-HCG therapy was carried out, ovulation was successfully induced. The serum estradiol levels were 144-2,700 pg/ml at the time of switching to HCG in these ovulatory cases. On the other hand, the levels were 56-292 pg/ml in the non-ovulatory cases. Furthermore, among the OHSS cases, the range of the serum estradiol levels for moderate OHSS was 577-2,400 pg/ml, while that of severe OHSS was 820-2,700 pg/ml. The serum estradiol levels of 8 cases which became pregnant were 532-2,700 pg/ml (Fig. 2).

2. Maximum follicular diameter (mFD)

1) Correlation with serum estradiol

We tried to find the correlation between mFD and serum estradiol levels for 88 cycles in

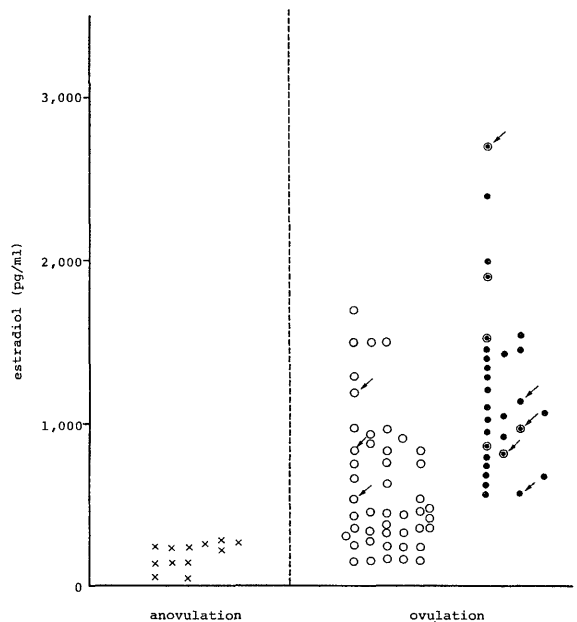


Fig. 2. The relation between the serum estradiol levels and ovulation or OHSS in 88 cycles (● OHSS, ◎ severe OHSS ↗ pregnancy).

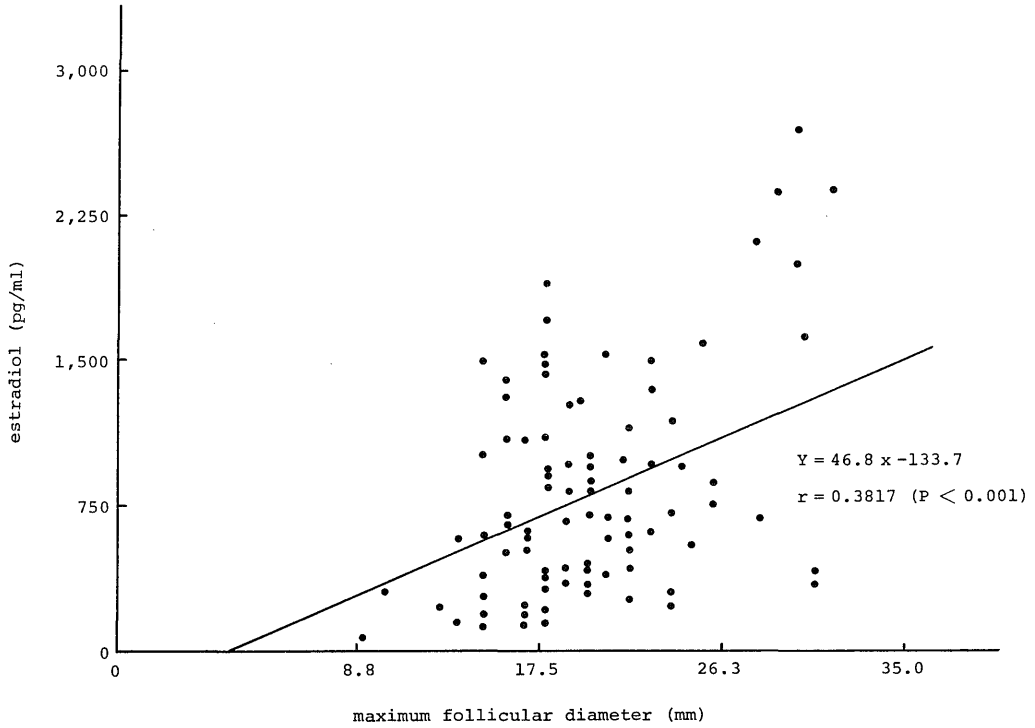


Fig. 3. Graph showing linear correlation between maximum follicular diameter and serum estradiol levels on the day switching to HCG.

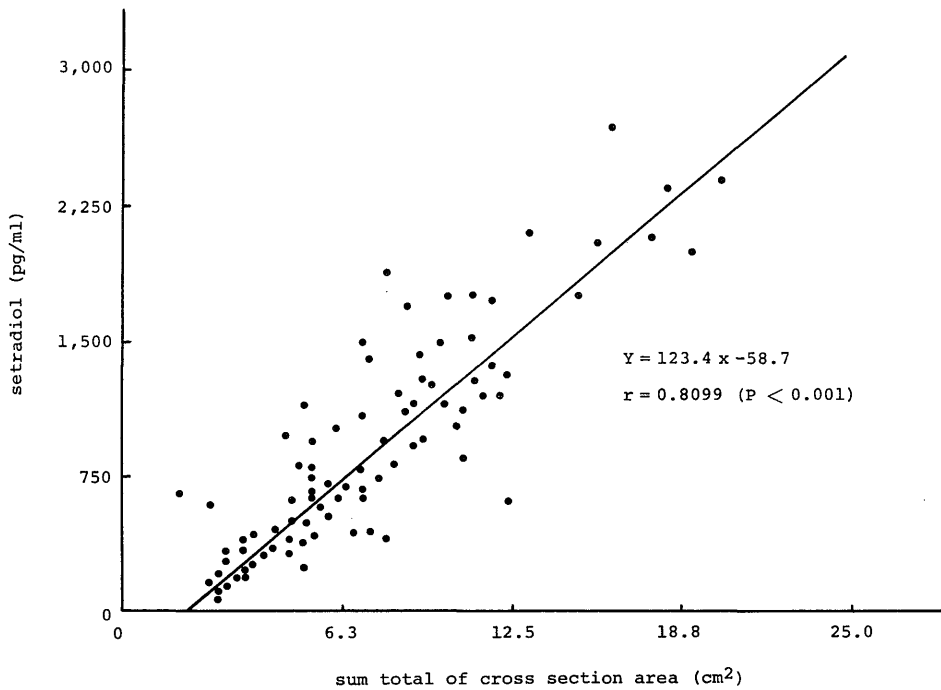


Fig. 5. Graph showing linear correlation between sum total of cross sectional area of follicles and serum estradiol levels on the day switching to HCG.

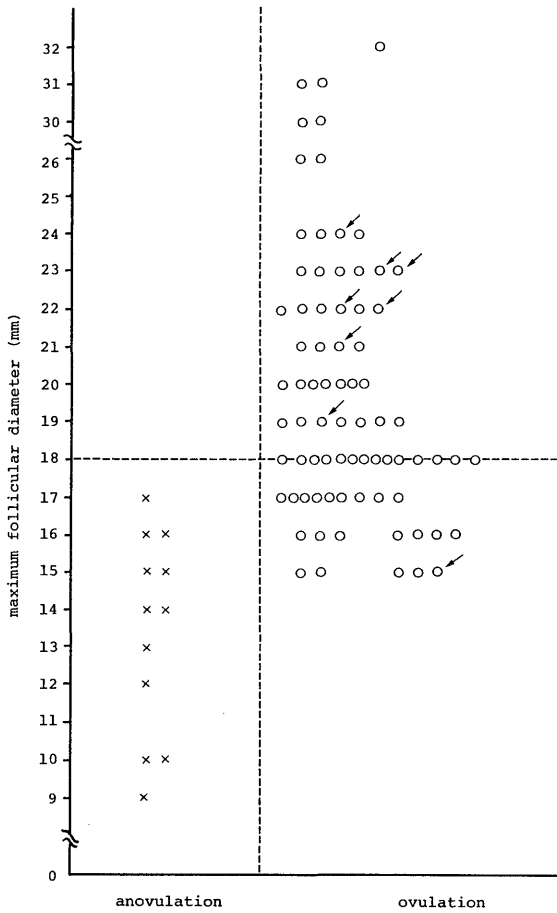


Fig. 4. Correlation with maximum follicular diameter and ovulation in 88 cycles (↗ pregnancy).

which we measured it at the time of switching to HCG, but we could not find a high correlation between them ($r=0.3817$) (Fig. 3).

2) Correlation with ovulation

After examining the correlation between mFD and ovulation in 88 cycles, we found that the minimum level of mFD at which ovulation occurred was 15mm and ovulation occurred in all cases where the follicular diameter was more than 18mm (Fig. 4).

3. Sum total of cross sectional areas of all follicles (FA)

1) Correlation with serum estradiol

The correlation coefficient between FA and serum estradiol levels in 88 cycles was 0.8099, so we found a high correlation between them.

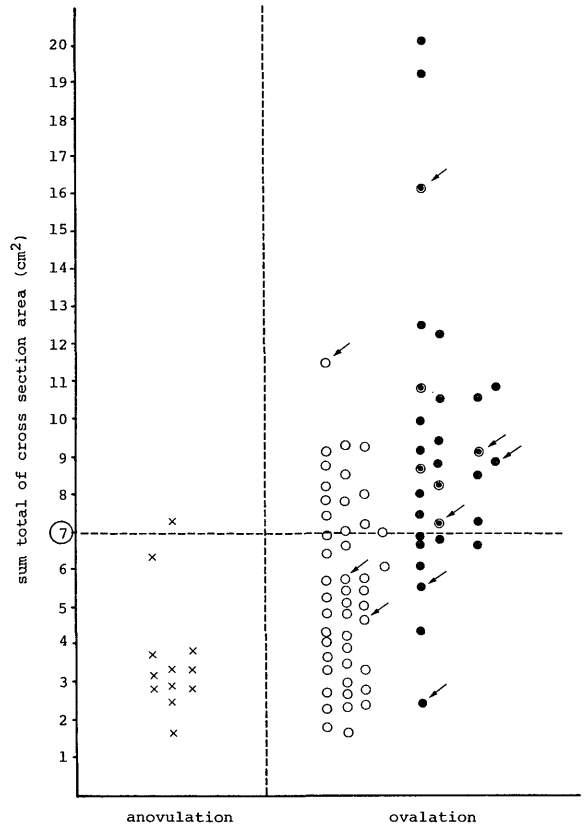


fig. 6. The relation between sum total of cross sectional area of all follicles in bilateral ovaries and ovulation or OHSS in 88 cycles (● OHSS, ● severe OHSS, ↗ pregnancy).

By using regression coefficients, FA 7.0cm^2 was equivalent to approximately 800 pg/ml of the serum estradiol levels (Fig. 5).

2) Correlation between ovulation and OHSS
The range of FA in 76 ovulatory cycles was $1.6\text{-}20.2\text{cm}^2$. On the other hand, the range of FA was $1.7\text{-}7.3\text{cm}^2$ in 12 cycles in which there was no ovulation, and FA in 30 cycles in which OHSS occurred was $2.5\text{-}20.2\text{cm}^2$. Severe OHSS, among these 30 cycles of OHSS, occurred in 6 cycles and the range of their FA was $7.2\text{-}16.2\text{cm}^2$ (Fig. 6).

DISCUSSION

1) The mechanism of OHSS occurrence

We think that prostaglandin (PG) and histamine are related to the occurrence of OHSS at the

time of HMG-HCG therapy. According to the reports by Pride *et. al.*³⁾, Chlorpheniramin (histamine-1 receptor blockade) and Pergonal were simultaneously administered to rabbits, and the weight of their ovaries, the quantity of ascites and the quantity of PG in ovaries were measured. Then they compared those weights, quantities and contents with a group of rabbits which were given only pergonal, and concluded that the direct effect of PG against OHSS occurrence is negligible, but PG is possibly concerned with OHSS occurrence through vasoactive substances such as histamine and so on. Now we see many reports that measurement of estrogen in urine and serum is useful to prevent OHSS occurrence. Therefore, we consider that estrogen is concerned in the mechanism of OHSS occurrence. Engel *et. al.*⁴⁾ mention an effect of estrogen as pathogenesis of OHSS, and Schenker⁵⁾ describes it as follows: OHSS occurrence can not be explained by only estrogen, nor is estrogen a main factor of OHSS occurrence. But as a large quantity of estrogen accelerates PG production, it is concerned in the mechanism of OHSS occurrence.

To think of the mechanism of OHSS occurrence mentioned above, we suppose that excessive estrogen accelerates PG production, which induce the secretion of vasoactive substances like histamine and so on, so that OHSS occurs by increased capillary permeability.

2) Prediction of OHSS occurrence

i) Comparison between assay of estrogen and USG

Too much estrogen is an indirect cause of OHSS, as has been stated. Therefore, if we measure the level of estradiol in urine and serum and establish the critical level for OHSS occurrence, we can prevent OHSS. Judging from the results with our patients, we can prevent severe OHSS, if we switch from HMG to HCG when the level is less than 800 pg/ml. However, the assay of estrogens entails cumbersome, timeconsuming procedures. Even if a rapid and simple method to measure estrogen is developed, it is difficult to judge each follicle's size (degree of maturity) from estrogen levels as a large number of follicles grow at the same time when using HMG therapy.

The same problem is pointed out by Smith *et.*

*al.*⁶⁾. On the other hand, USG is useful to establish when to induce ovulation (by changing from HMG to HCG) as each follicle's size can be determined by USG. Therefore, if USG makes it possible to predict OHSS, USG becomes a monitoring method combining both prevention of OHSS and induction of ovulation. Its clinical significance is quite big.

ii) Maximum follicular diameter (mFD)

It is hard to estimate estrogen level from mFD, as the correlation between mFD and serum estradiol level is quite low. Therefore, mFD can hardly become an indicator for OHSS. However, when we switched from HMG to HCG at the time when mFD was larger than 18mm, we found ovulation in all cases, so that mFD is quite useful as a parameter to decide when to induce ovulation by HCG. From the view point of minimizing the number of ovulations and preventing OHSS, it would be advantageous to change to HCG at the time when follicular diameter reaches the minimum limit (mFD 15mm) at which it is possible to ovulate. But all mFD at the time, switching to HCG, were larger than 19mm in pregnant cases. McNatty *et. al.*⁷⁾ recently reported that only follicles of 18 to 25mm had a granulosa cell complement consistent with impending ovulation. However, they point out that when the diameter is smaller than 18mm or larger than 25mm, the number of granulosa cells decreases. Therefore, it is proper to change to HCG when mFD is about 18-19mm, in case of inducing ovulation for the purpose of conception. However, there exists a time lag of more than 24 hours between the time of switching to HCG and the time of ovulation. Therefore, mFD is supposed to be larger than 20mm at ovulation even though we change from HMG to HCG when mFD is 18mm.

iii) Sum total of follicular cross sectional area (FA)

At the time when HMG was administered, serum estradiol level represents the sum total of estrogen which is secreted from many developed follicles, and the sum total of follicular volume reflects serum estradiol level well⁸⁾. So, if we measure the sum total of follicular volume by USG, we can guess the serum estradiol level and it becomes a predictive parameter for the occurrence of OHSS. However,

as it is troublesome and also technically difficult to measure so many follicles' volumes by USG, it is hard to use this method daily in the clinics, so we substituted the follicular cross sectional area. It is supposed that the total of follicular cross sectional area (FA) and serum estradiol levels are strongly related, and FA reflects serum estradiol level well. Though moderate OHSS occurs when FA is less than 7.0cm^2 , no severe OHSS occurs and moderate OHSS is not a big problem clinically. Therefore, if we switch to HCG with the criteria that FA is less than 7.0cm^2 and mFD is larger than 18mm, we can certainly induce ovulation without severe OHSS. If we stop giving HCG without consideration for follicular diameter when FA is larger than 7.0cm^2 , we can prevent severe OHSS occurrence.

Though 19 cases out of 76 ovulatory cycles (25%) did not satisfy these criteria, OHSS occurrence was not recognized. Therefore, if we use these criteria, it means that we would not give HCG to cases which would have probably been normal. This tells us that the appropriate effective dose of HMG easily induces OHSS, that is, HMG is an agent having a relatively small margin of safety between successful induction of ovulation and OHSS occurrence. This is a subject to be improved in the future.

Here we introduced the use of aum total of follicular cross sectional area by USG as an indicator for predicting the occurrence of OHSS and discussed its usefulness. Monitoring of follicular development by USG is easy and rapid, so that it will become an indispensable examination for induced ovulation by gonadotropin.

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