A CASE WHO BECAME PREGNANT WITH SYMPTOM OF
ACUTE ABDOMEN AS THE RESULT OF OVULATION
INDUCED WITH PMS AND HCG

SEIICHI MATSUMOTO AND KODO TOHMA

Department of Obstetrics and Gynecology, School of Medicine,
Gunma University, Maebashi

Efficacy of combined administration of PMS and HCG for induction of ovulation has been recognized by many workers since Hamblen (1941), and Rydberg (1943). On the other hand, however, Schochaert et al. (1956), Reymond et al. (1959), Müller and Bader (1959) and others (Rydberg, 1942; Thaysen, 1943; Davis, 1944; Soggaad, 1944; Palmer, 1954; Petersen, 1946; Cole, 1948; Movin, 1949 and 1949; Petersen, 1948; Madsen 1949; Rijsfeldt, 1949; Gotzsche, 1951; Jorgensen, 1951; Boddart et al., 1956; Combes-Hamelle, 1957; Ezes, 1957; Le dall, 1957; Figueroa Casas, 1958; Vandiest, 1958; Matsumoto, 1960; Rosenberg et al., 1960; Mitani et al., 1962) observed its side effects, especially acute abdomen resulting from over-stimulation, and Béclère (1959) issued warning against its use. Further, workers have been critical of gonadotrophin therapy because it brings about lower rate of pregnancy compared with other method of ovulation induction. Especially few cases have been reported to become pregnant as the result of artificial ovulation with heterogenous preparations (Jones 1961). Only lately, Gemzell et al. (1958), Rosenberg et al. (1960), Gemzell (1961 and 1962), Buxton (1961 and 1963) and Crooke et al. (1964) attempted to elevate pregnancy rate by the use of human pituitary gonadotrophin (HPG) and bright future is now being opened for gonadotrophin therapy.

Recently we attempted combined administration of PMS and HCG in an amenorrhoeal patient, and during the treatment she developed acute abdomen as the result of over-stimulation. By laparotomy we found bilateral ovarian tumors and multiple ovulation and performed wedge resection of ovaries, but happily she became pregnant, being successfully delivered at term. The object of the present paper is to give report on this case.

CASE REPORTS

Patient

The patient was a 27-years-old sterile woman. Since menarche in the age of 13 years, she had relatively normal menstrual cycle. After marriage at 24 years of age, however, menstruation took place only for 3 months, and she became
amenorrhoea after June 1960. Thereafter she received from time to time hormone therapy, which induce bleeding each time.

In the middle of May 1962, hormone injection induced 3-day bleeding, but thereafter amenorrhoea again persisted. On September 14, 1962 she visited our hospital with complaint of 4 years absence of spontaneous menstruation. There was nothing particular either in her family or past history.

**Findings at first examination**

Stature 153 cm, span 150 cm, body weight 45 kg, chest circumference 67 cm, loin circumference 88 cm. She had rather slender type, normal physiognomy, normal hairiness, no anemia, and medium growth of the breast. Both moral and intellectual ability were satisfactory.

Pubic hair was of medium growth, rather of masculine type, external genitalia normal. Pelvic examination revealed normal vagina, rather posteriorly flexed and small-sized uterus. Adnexa uteri were not palpable. Specular examination showed the portio vaginalis uteri to be small, but no erosion.

**Course of treatment**

Basal body temperature (BBT) was monophasic, and intramuscular injection of 10 mg progesterone failed to induce bleeding (negative gestagen test). Combined administration of 10 mg estradiol dipropionate and 125 mg hydroxyprogesterone capronate could induce bleeding (positive E.P. test).

Thereupon ovulation induction was attempted by oral administration of Bellergal (mixture of Belaphorin, ergotamine tartrate and phenobarbital) for about 2 months starting on October 8, 1962, but in vain. From February 5, 1963, Kaufman therapy (cyclic combined administration of estradiol dipropionate and hydroxyprogesterone capronate) was attempted, but even after completion of this therapy, ovulation could not be elicited. Various endocrinological assays performed from April 26, 1963 gave results as shown in Table 1. In view of low urinary 17-OHCS level evidenced in them, 10 units of ACTH was intramuscularly given every other day from April 26 to June 21, 1963, but the administration was

<table>
<thead>
<tr>
<th>Table 1. Laboratory findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
</tr>
<tr>
<td>April 26, 1963</td>
</tr>
<tr>
<td>Urinary gonadotropin</td>
</tr>
<tr>
<td>Smear index</td>
</tr>
<tr>
<td>Urinary 17 KS</td>
</tr>
<tr>
<td>Urinary 17 OHCS</td>
</tr>
<tr>
<td>PBI</td>
</tr>
<tr>
<td>BMR</td>
</tr>
<tr>
<td>normal range</td>
</tr>
<tr>
<td>Smear index</td>
</tr>
<tr>
<td>17 KS</td>
</tr>
<tr>
<td>17 OHCS</td>
</tr>
</tbody>
</table>
discontinued since no remarkable change was observed either in BBT or in cervical mucus. So gonadotrophin therapy according to ITP method (Igarashi et al., 1957) was started on June 25 (Fig. 1). First, PMS (Serotropin, Teikoku Hormone Mfg., Tokyo) was intramuscularly injected for 9 days in a daily dose of 1,000 I.U., and cervical mucus was subsequently increased to 600 cm². In succession, each 1,000 units of PMS and HCG (Primogonyl, Schering A.G., Berlin) were concurrently given by intramuscular route for 2 days, which was followed by intramuscular injection of 1,000 units of HCG for 2 days. In the evening before the day of the last injection, the patient felt tension in the lower abdomen. Examination on July 7, 1963 could not find any subjective symptoms indicating acute abdomen, but pelvic examination disclosed that the uterus was small, while the left ovary was swollen to egg size, and the right ovary to fist size, each causing tenderness. Instantly the therapy was discontinued, and the patient was allowed to return home with prescription of absolute rest. About 10 days later, she visited this hospital accompanied by her mother with complaint of serious distension of the lower abdomen. At that time she was not yet in shock state, but there were pallor and expression of agony on her face. Without losing time she was hospitalized.

**Findings on admission**

Consciousness clear, respiration normal, pulse rate 108/min. with satisfactory tension, blood pressure 110–65 mm Hg, no anemia in the palpebral conjunctiva and no abnormalities in the bulbar conjunctiva. Heart sound clear, and lung field normal, but the abdomen as a whole showed serious distension and tension with dull sound. Especially in the left lower abdomen a tumor was palpable.

**Fig. 1.** BBT, Cervical mucus and smear index during the gonadotrophin therapy
having strong tenderness. Hematological findings; red cells $453 \times 10^4$, hemoglobin (Sahli) 85%, and white cells 13,000. Urinary examination; both protein and sugar negative.

On the basis of the above mentioned findings, we made diagnosis of acute abdomen due to gonadotrophin therapy, and performed laparotomy on the following day.

**Findings at laparotomy**

1) Peritoneal space was filled with about 2,500 cc of yellow, transparent, gelatinous serum, which spurted out on the laparotomy.

2) The uterus had nearly the normal size but the right ovary was swollen to the size of a child's head, and the left to a large fist-size, both having surface dark reddish purple and uneven, and both being extremely soft and fragile. Here and there thumb tip-sized follicles could be seen through, and especially on the surface of the right ovary there were some places where leaks of follicular liquid were seen. But ovarian bleeding was not visible (Fig. 2).

![Fig. 2. Findings at laparotomy](image)

Both ovaries are remarkably enlarged.

**Table 2. Nature of follicular fluid**

<table>
<thead>
<tr>
<th>Protein</th>
<th>4.0 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolytes</td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>4.3 mEq/l</td>
</tr>
<tr>
<td>Na</td>
<td>141.0</td>
</tr>
<tr>
<td>Ca</td>
<td>4.5</td>
</tr>
<tr>
<td>Cl</td>
<td>127.0</td>
</tr>
</tbody>
</table>
3) About 20~30 cc of follicular liquid was obtained through puncture of each large follicle. It had properties as shown in Table 2, and gelatinized under the cold place.
4) Wedge resection reduced the both ovaries nearly to egg size.
5) About 9 fresh corpora lutea were observed in resected ovarian tissue

Fig. 3. Masses of luteinized theca cells and small cysts with the distended follicles.
sections. Histological observation (Fig. 3) disclosed many aggregations of luteal cells, which were derived from theca cells through luteinization, and further small vesicles, which were formed as the result of distension of follicles.  

6) In the peritoneal space was accumulated in total 3,130 cc. of liquid. And the amount of bleeding due to the operation was 430 cc. The postoperative course was satisfactory. Because of lack of withdrawal bleeding after operation, Friedman reaction was performed on August 1, 1963 (14th postoperative day), with result of 200 rabbit unit positivity. The second reaction on August 11 also gave 200 rabbit unit positivity, indicating the occurrence of pregnancy. Thereafter BBT continued to be high, and the patient was discharged after 25 uneventful postoperative days. The course after the discharge was also satisfactory, with only slight morning sickness and without complication of toxemia of pregnancy. Abdominal rentgenography at 32 weeks of pregnancy confirmed a single fetus. On April 7, 1964, the patient was delivered of a girl in II vertex presentation. The course of delivery is shown in Table 3. The newborn had no malformation, and both the placenta and umbilical cord were normal as shown in Figure 4. Now one month has passed uneventfully after the delivery, and the newborn continued normal growth.

<table>
<thead>
<tr>
<th>Table 3. Course of delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of labor</td>
</tr>
<tr>
<td>Rupture of membranes</td>
</tr>
<tr>
<td>Apparition</td>
</tr>
<tr>
<td>Crowning</td>
</tr>
<tr>
<td>Delivery</td>
</tr>
<tr>
<td>Expression of placenta</td>
</tr>
<tr>
<td>1st stage</td>
</tr>
<tr>
<td>2nd stage</td>
</tr>
<tr>
<td>3rd stage</td>
</tr>
<tr>
<td>Blood loss</td>
</tr>
</tbody>
</table>

DISCUSSION

It is known that pregnant mare serum gonadotrophin (PMS) has follicle stimulating activity just like pituitary FSH and human chorionic gonadotrophin (HCG) has luteining activity just like pituitary LH. Many attempts have been made to induce ovulation by the use of these hormone preparations, and their efficacies have been recognized. However, with extensive use of a large dose of this heterogeneous gonadotrophin, which was originally introduced by Rydberg (1943), swelling or other hyperreaction of the ovary was observed as the result of this therapy, especially complication of acute abdomen was reported in European countries—26 cases by Bèclère (1960), each one case by Figueroa Casas (1958), Matsumoto (1960) and Mitani et al. (1962), totalling 29 from 1942 to the present. These reports are summarized in Table 4. The incidence rate and number of cases vary from one author to another.
Fig. 4. Newborn and the placenta
According to the review by Béclere (1960), ages of the 26 cases ranged 13 to 35 years, and the abnormal response of the ovary tended to occur with predilection in young women. As for diagnosis before starting gonadotrophin therapy, his 20 cases had amenorrhoea (mostly idiopathic), and the remaining 6 had sterility as chief complaint.

In Japan, Mitani et al. (1962), observed enlargement of the ovary in 2 of 24 cases, treated with gonadotrophin and one of them was subjected to laparotomy with the diagnosis of appendicitis. Matsumoto (1960) performed gonadotrophin therapy with 87 cases, one of whom had been subjected to bilateral ovariectomy by a surgeon with misdiagnosis for acute appendicitis.

The clinical picture somewhat varies from case to case, but at least those subjected to laparotomy all manifested common feature as Béclere indicated. The present case was not an exception in this respect. Abdominal pain indicative of this morbidity generally develops at 8 to 14 days after the first injection of the hormone, and it was on the 12th day that the present case visited our hospital with complaint of abdominal pain. The abdominal pain sometimes exacerbates progressively, and gas evacuation. The abdomen is distended with strong tenderness, and dull sound is audible on the lateral side. Pelvic examination and palpation on the abdomen generally show, besides pain and bulging of the intestinal loop, presence of one or two tumors in the pelvic or peritoneal cavity. The size of the tumor ranges from mandarin- to melon-size.

The patient often manifests evident symptom of shock or internal hemorrhage, and has pallor on her face and pointed ala nasi, fast beating pulse and such low temperature as causes coldness of extremities.

In many occasions various erroneous diagnoses are made in the commencement with regard to this acute abdomen owing to the site of pain and serious accompanying symptoms. For examples, 4 cases were reported abroad to have been diagnosed as acute appendicitis because of the pain confined to the right side; 2 cases were diagnosed as intestinal obstruction because of vomiting and
perfect stop of defecation and gas evacuation and remarkable bulging of the intestinal loop; 3 cases were considered to have rupture of tubal pregnancy on the ground of unconsciousness, shock symptom and internal hemorrhage; 7 cases rupture of ovarian tumor on the ground of palpation of abnormal tumor in the pelvis at the site of the ovary; and one was mistaken for torsion of the stalk of ovarian cystoma on account of severe pain and shock symptoms; besides these, 5 were treated, without sufficient evidences, simply as subacute abdomen.

Samely as clinical findings, observations at laparotomy have also characteristic features though varying in their grades: Superovulation in the swollen ovary, and accumulation of serous liquid (sometimes serous sanguineous liquid), often amounting to above 2 l, which is the cause of dull sound on the lateral abdomen; ovaries always swollen bilaterally though varying in degree from case to case, ranging from goose egg size to fist or kidney size (2 times the size of the fist in the present case), and in rare occasions being as large as the head of the adult, but nearly equal on both sides; and macroscopically they always present reddish purple color, are soft and fragil with irregular uneven surface owing to bulging and protrusion of large and small follicles; some large follicles can be seen through from outside, and sometimes leaks of serous bloody liquid are observed through rupture of the ovarian surface. Section surface of the ovary presents a picture similar to placental tissue, having numerous scattered corpora lutea. In the present case, the wedge resected tissue contained 9 fresh corpora lutea and it was microscopically observed that numerous follicles formed small vesicles through distension. The present case was further characterized by a small number of interstitial edema and strong hyperemia of the vessel.

Out of these 29 cases, 23 were subjected to emergent surgical operation. Bilateral ovariectomy was performed in 6 cases and total hysterectomy with bilateral ovariectomy was performed in another case. In the other cases, tissues of ovarian hilus were able to be preserved. Other nine cases were treated by unilateral ovariectomy, puncture of vesicles, suture of ruptured part as well as by partial resection. Only one case was treated just by simple suture. Just 6 cases out of the total 29 were conservatively treated, and 4 cases of these 6 were treated with testosterone administration. All of them were restored to the normal state within several weeks. Out of these 29 cases, 2 died, the one from ovarian tumor complicated with intestinal obstruction, and the other (Figueroa Cases, 1958) from superfist-sized tumor complicated with anuria and leucocytosis 24 hrs. after laparotomy.

It was reported (Ikegawa et al., 1957) that ovarian tumor was observed more or less in almost all the cases who received gonadotrophin, especially combined administration of PMS and HCG. According to Keetel and Bradbury (1957) and Ikegawa et al. (1957), however, many of them were restored to the normal within about 2 weeks while observed without any treatment. Matsumoto (1960) reported that it took about 2 months for a case to restore. When laparotomy must be performed on account of ovarian tumor, it is advised by Müller and Bader (1959), for the consideration of future gestation, to preserve ovarian tissue, even if partly, and to leave the uterus and tube intact. In recent days, treatments are generally made along this line.
The cause of these abnormal enlargement of the ovary is evidently the result of gonadotrophin administration, putting aside the sensitivity of the patient. And it is necessary to remember that since they developed after prevalent use of Rydberg's massive administration, there must have surely been cases receiving overdoses. Rydberg himself reduced the total dose of HCG in 3 injections of 15,000 i.u. after he observed damages produced by his initial method. Other workers also use similar doses—PMS 5,000 i.u.×2, followed by HCG 10,000 i.u.×3. Béclère (1959) found by analysis of 26 case reports: even small doses of PMS induced abnormal ovarian enlargement in 4 cases, among which 3 cases showed subacute symptom and were cured by conservative treatment. In these 3 cases the doses of PMS were 4,200 i.u., 5,000 i.u. and 7,500 i.u. respectively. The remaining one case, administered 5,000 i.u. of PMS, needed surgical treatment, partial resection of the enlarged ovaries.

In the 26 cases that needed total or partial ovariectomy, the average doses of administered PMS were from 10,000 i.u. to 15,000 i.u. Further he reported that the minimum dose for subacute symptom was PMS 5,000 i.u. and HCG 3,000 i.u. On the other hand we find deep interest in the fact that it is after the administration of HCG that ovarian tumor is clinically observed. In the experiment using hypophysectomized rat, (Igarashi et al., 1962), administration of FSH, LH or HCG alone did not induce any formation of corpus luteum, while combined administration of FSH and LH or of FSH and HCG induced it. And it is reported that by synergism between these two kinds of hormone, ovarian stimulating effect will be elevated to the maximum. Also in human subjects, it seems natural to assume that ovarian tumor will be produced by synergism between PMS and later administered HCG, since the former is delayed in excretion. There is report (Reymond et al., 1959) on a 16 years old girl in whom acute abdomen was induced by simple administration of 15,000 units of HCG. This seems highly probable if we consider that there is hypergonadotrophic amenorrhoea as reported by Béclère (1963) and Matsumoto and Ozawa (1964) and that in this case before the administration of HCG, follicles must have attained sufficient maturity in the presence of FSH. This suggests that in the induction of ovulation with gonadotrophin, there is highest danger of acute abdomen when HCG is given in succession to or in association with FSH.

It goes without saying that in order to avoid this, daily pelvic examination is necessary. But at the same time it is important to select adequate method with reference to individual difference in sensitivity to gonadotrophin. From this view point, Igarashi and Matsumoto's Identified Two Phasic (ITP) method (1957) is recommendable, in which gonadotrophin is administered in 2 steps considering individual difference in follicle maturity, which is assayed by cervical mucus amount. In effect, the ovarian enlargement developed only in 3 of 87 cases treated by this method (Matsumoto et al., 1963).

Now, gonadotrophin therapy was reported effective for cases with hyperestro-genism (Hamblen and Davis, 1945), for polycystic ovary (Staemmler, 1956), for cases in whom estrogen is remarkably increased by gonadotrophin administration, and especially effective for secondary amenorrhoea after parturition (Dörfller and Steammler, 1957). As for the method of its administration, Westman (1940), Rydberg
(1942), Rydberg and Pedersen-Bejgaard (1943), Hamblen and Davis (1945), Westman (1940), Staemmler (1956) and Igarashi and Matsumoto (1957) reported their respective devices and results of applications. However, despite their theoretical plausibility, practical results in pregnancy rate are not always satisfactory. There are few reports on successful artificial ovulation with heterogeneous gonadotrophin which was immediately followed by gestation. Jones et al. (1961), who performed gonadotrophin therapy with 52 cases, reported that it was successful only in 3, but they did not give any further detail. It is reported that in cows and horses, many ova after ovulation with gonadotrophin are immature (Imamichi and Nobusawa, 1963). Assumably pregnancy will not be attained in human beings even after ovulation if ova induced with gonadotrophin are not mature enough for fertilization as in these animals.

Mandelstamm (1932) recognized that ovulation induced by gonadotrophin was multiple, but it still remains in obscurity why there is difference between physical and gonadotrophin-induced ovulation. Will there be any difference in the action or amount of gonadotrophin? Since multiple ovulation was observed after administration of human hypophysial gonadotrophin (Buxton, 1961 and 1963) the procedure of hormone preparation will have no bearing on it.

In the present case, administration of gonadotrophin was discontinued immediately after discovery of ovarian tumor, but nevertheless it exacerbated progressively, attaining the peak about 10 days later. It is not clear whether this occurred owing to the long lasting effect of the administered preparation or it resulted from activation of endogenous gonadotrophin through some mechanism.

<table>
<thead>
<tr>
<th>Table 5. Important points in Gonadotropin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Indication and contraindication</td>
</tr>
<tr>
<td>2. Method of treatment</td>
</tr>
<tr>
<td>3. Multiple ovulation</td>
</tr>
<tr>
<td>4. Low pregnancy rate</td>
</tr>
<tr>
<td>5. Side action</td>
</tr>
<tr>
<td>i) Allergic action</td>
</tr>
<tr>
<td>ii) Production of antihormone</td>
</tr>
<tr>
<td>iii) Hyperluteinization</td>
</tr>
<tr>
<td>6. High value</td>
</tr>
</tbody>
</table>

Other problems concerning gonadotrophin therapy are shown in Table 5. As to establishment of allergy or production of antihormone, the present dose is not considered significant enough to raise any suspicion (Matsumoto, 1962).

As to the problem of hyperluteinization, we must of course avoid overdose, but it seems to be dependent of sensitivity of the ovary to gonadotrophin or indication. According to Staemmler (1956), it may be considered that gonadotrophin is apt to become hyperactive in such cases.

In the end we want to refer to the results of various tests performed with the present case before starting gonadotrophin therapy. She had medium constitution,
and the bilateral adnexa could not be palpated during pelvic examination despite the presence of tumor. She had so-called grade II secondary amenorrhoea, in which gestagen test does not induce bleeding. According to endocrinological assay, thyroid function was nearly normal, urinary gonadotrophin low, smear index —2.6 with low estrogen activity, and urinary 17KS was rather high, while urinary 17OHCS was low, indicating hyperandrogenic ovarian insufficiency (Matsumoto et al. 1962). There was, however, no definite clinical evidence of Stein-Leventhal syndrome. In Metopiron test, urinary 17OHCS level was abnormally high with pyrexia, indicating disorder of hypothalamus (hypersensitive). Considering these results, it can not be denied that the employed dose of gonadotrophin was too large for the present case. Since, however, she became pregnant after this therapy, it can also be assumed that just this overdose must have been responsible for producing mature follicles in the optimal state for fertilization. And bilateral wedge resection of the ovary may have further induced hyper-release of endogenous LTH to activate corpus luteum of pregnancy, thus giving good effect on implantation of fertilized ovum and for its growth. At any rate the present case is considered to give an important clue for the problem of inducing ovulation and pregnancy by means of gonadotrophin. And the fact that single pregnancy took place despite multiple ovulation seems to suggest that the maturation stage of the ova in the multiple follicle was different each other.

SUMMARY

When, PMS heterogenous gonadotrophin, was administered to the amenorrhoic women, the rate of pregnancy was not so high despite considerable high rate of ovulation. This has been a question up to date.

Recently we performed combined gonadotrophin therapy of PMS and HCG on a 27-years-old woman with grade II secondary amenorrhoea, and succeeded in inducing ovulation. But owing to overstimulation by PMS and HCG therapy, she developed complication of acute abdomen. Thereupon laparotomy was performed to carry out wedge resection on the ovary. At the time of this induced ovulation, the patient succeeded in pregnancy which continued until term inspite of the ovarian operation. At term she was delivered of a normal child. We made some comments on this case.

REFERENCES

Sept. 1965

ACUTE ABDOMEN BY INDUCED OVULATION

171


Imamichi T. and A. Nobusawa (1963). Personal communication


Matsumoto, S. and M. Ozawa (1964). Personal communication


