Comparison of endocrinological stress response associated with transvaginal ultrasound-guided oocyte pick-up under halothane anaesthesia and neuroleptanaesthesia

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Twelve patients with mechanical infertility in the in vitro *fertilization program were studied. Seven of them received halothane anaesthesia and the other five received neuroleptanaesthesia. Higher plasma prolactin levels and lower plasma progesterone levels were observed in the neuroleptanaesthesia group than in the halothane group during and after transvaginal ultrasound-guided oocyte pick-up. Plasma adrenocorticotropic hormone and cortisol levels of the patients suggested that surgical stress was minimal in both groups. It is likely that droperidol and fentanyl, both used in neuroleptanaesthesia, were responsible for the hyperprolactinaemia which was followed by inhibition of progesterone production. These agents, therefore, are not recommended as anaesthetic agents for transvaginal ultrasound-guided oocyte pick-up.*

Key words

ANAESTHESIA: gynaecological; ANAESTHETICS, INTRAVENOUS: droperidol, fentanyl; ANAESTHETICS, VOLATILE: halothane; HORMONES: adrenocorticotropic, corticosteroid, luteinizing, progesterone, prolactin.

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The endocrinological milieu during oocyte retrieval has been considered an important factor to determine the success rate of *in vitro* fertilization (IVF).[1] It has been suggested that hyperprolactinaemia during laparoscopic oocyte recovery for IVF under general anaesthesia[2] causes the luteal insufficiency and reduces the success rate of IVF.[3] In recent years transvaginal ultrasound-guided oocyte pick-up has become popular and one of the advantages of this technique over the laparoscopic oocyte recovery is the lower plasma prolactin (PRL) levels during the transvaginal technique than those during laparoscopy.[2,4] There have been few reports on the influence of anaesthetic agents used for the transvaginal ultrasound-guided oocyte pick-up on plasma PRL and other hormone levels during the procedure. The present study was undertaken to compare the influences of two anaesthetic techniques, one using halothane and the other using neuroleptanaesthesia, on plasma PRL, progesterone (P), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH) and cortisol concentrations during and after transvaginal ultrasound-guided oocyte pick-up. Plasma concentrations of human chorionic gonadotropin (hCG) which was administered at the time of oocyte retrieval to provide mature oocyte were also monitored.

Methods

Following approval from the Committee on Human Research of Kyoto University and informed consent of the patients, we studied 12 patients (26–38 yr) with mechanical infertility in the IVF program. All patients showed that their basal plasma PRL levels were within the normal range (<30 $ng \cdot ml^{-1}$) and were ASA Physical Status

Class I. They underwent stimulation of ovulation with clomiphene citrate/human menopausal gonadotropin (HMG)/hCG, as described elsewhere.[5] In brief, patients received 50–100 mg clomiphene citrate from day two of the menstrual cycle for five days followed by daily injection of 150 IU of HMG. The HMG was discontinued when follicle diameter measured by ultrasonography reached 15–18 mm, and 5000 IU of hCG was administered 52 hours after the last HMG injection. Anaesthesia for transvaginal ultrasound-guided oocyte pick-up was started usually at 1000 h, 36 hours after the injection of hCG. On the day of oocyte pick-up, patients received premedication with atropine sulphate (0.5 mg) 30 min before the induction of anaesthesia (at 0930 h), and they were randomly assigned to one of the two groups for the study. Patients in Group I (halothane group, $n = 7$) received thiopentone (5 $mg \cdot kg^{-1}$) and succinylcholine chloride (1 $mg \cdot kg^{-1}$) IV and anaesthesia was maintained with nitrous oxide (66 per cent), oxygen (33 per cent) and halothane (0.5–1.0 per cent) after tracheal intubation. Patients in group II (neuroleptanaesthesia group, $n = 5$) received droperidol (0.1 $mg \cdot kg^{-1}$) and fentanyl (4 $\mu g \cdot kg^{-1}$) IV and an additional 50–100 mg of thiopentone was administered IV immediately before puncture of the vaginal wall. Patients in Group II did not receive supplemental oxygen administration. The vaginal wall puncture was performed approximately 30 min after the induction of anaesthesia in both groups. From each patient, blood samples were drawn through an indwelling catheter immediately before the induction of anaesthesia, 30 min after induction, at the end of oocyte pick-up (usually one hour after the induction), four, seven and 24 hours after the induction of anaesthesia. Blood samples were collected into chilled glass tubes containing EDTA-2Na, and immediately centrifuged at 4° C. Plasma samples were stored at −20° C until assayed.

Plasma PRL and cortisol concentrations were measured by radioimmunoassays (RIAs), as previously described.[6,7] Plasma P concentration was also measured by RIA, employing commercial kit supplied by CIS-Atomic Energy Lab. of Biomedical Products (Gifsur-Yvette, France). The minimal detectable value was 0.2 $ng \cdot ml^{-1}$ by this method. Plasma ACTH concentration was measured by RIA without extraction using anti-ACTH antiserum "IgG-ACTH-1" (IgG Corporation, Nashville, TN)[8] and human ACTH (1-39) (Peninsula Laboratories, Belmont, CA) as the standard. The minimal detectable quantity by this method was 10 $pg \cdot ml^{-1}$. Plasma LH and hCG concentrations were measured by enzyme immunoassay (EIA) kits using monoclonal antibodies obtained from Mochida Pharmaceutical Co., Tokyo. The cross-reactivity of hCG to LH EIA was less than two per cent and that of LH to hCG EIA was less than one per cent. The minimal detectable value was 5 $mIU \cdot ml^{-1}$ in both kits. Intra- and inter-assay coefficients of variation of these RIAs and EIAs were within ten per cent.

TABLE I Changes in vital signs

	Group I ($n = 7$)	*Group II* ($n = 5$)
Age (yr)	32.3 ± 1.7	30.0 ± 1.4
Body weight (kg)	49.6 ± 1.4	51.4 ± 1.3
Heart rate (min^{-1})		
Before induction	87.4 ± 4.9	86.6 ± 5.4
0.5 hr after induction	78.6 ± 2.1	80.8 ± 3.7
Mean arterial pressure (mmHg)		
Before induction	89.0 ± 3.0	85.7 ± 3.9
0.5 hr after induction	88.0 ± 5.6	83.4 ± 1.5

All values are mean ± SE of each group.

Repeated measurement ANOVA was used for the statistical analysis of hormone concentrations and the comparison of mean values was performed by the Bonferroni method.

Results

There was no statistical difference in the vital signs of the two groups during oocyte pick-up (Table I). Slight decreases of heart rate were observed in both groups after induction of anaesthesia but the differences from each control value before induction of anaesthesia were not significant. No changes were observed in mean arterial pressures of both groups after induction of anaesthesia and heart rates and mean arterial pressures were not affected by the vaginal wall puncture which was performed 0.5 hour after induction of anaesthesia. Lung ventilation was assisted manually in Group I, and no airway obstruction was observed in Group II. Neither hypoxaemia nor hypercarbia was observed in the two groups during the surgical procedure ($PaCO_2$, Group I: 38.4 ± 1.5, Group II: 41.9 ± 1.1 (mean ± SE) mmHg and PaO_2, Group I: 170.7 ± 10.9, Group II: 97.2 ± 3.9 mmHg).

Plasma hormone levels throughout the experimental period are shown in Table II. Plasma hormone concentrations before the induction of anaesthesia did not significantly differ between the two groups. Following the induction of anaesthesia, plasma PRL levels increased significantly, remained high up to four to seven hours and returned to the basal level 24 hours after the induction of anaesthesia. The magnitude and duration of PRL secretion were greater in Group II and plasma PRL levels were significantly higher in Group II than Group I until seven hours after the induction of anaesthesia. Plasma P levels were virtually unchanged up to seven hours but significantly increased 24 hours after the induction of anaesthe-

TABLE II Changes in plasma PRL, P, LH, hCG, ACTH and cortisol concentrations during and after transvaginal ultrasound-guided oocyte pick-up

		Before induction	*After induction of anaesthesia*				
			0.5 hr	*1 hr*	*4 hr*	*7 hr*	*24 hr*
PRL	Group I	19.3 ± 2.5	52.4 ± 4.2*	39.9 ± 2.5*	28.3 ± 4.7	20.7 ± 1.4	26.4 ± 5.3
($ng \cdot ml^{-1}$)	Group II	28.0 ± 2.0	230.0 ± 36.0*†	195.8 ± 41.0*†	88.0 ± 6.1*†	65.8 ± 3.9*†	18.4 ± 2.1
P	Group I	4.8 ± 0.7	6.1 ± 0.9	6.1 ± 0.8	4.9 ± 0.5	5.9 ± 0.6	12.5 ± 1.2*
($ng \cdot ml^{-1}$)	Group II	3.3 ± 0.5	3.2 ± 0.5†	2.7 ± 0.5†	3.2 ± 0.5†	3.6 ± 0.6†	5.3 ± 1.2*†
LH	Group I	39.8 ± 8.4	44.0 ± 12.2	36.7 ± 7.0	26.7 ± 3.5	21.0 ± 3.5	15.5 ± 4.2*
($mIU \cdot ml^{-1}$)	Group II	42.8 ± 5.1	41.1 ± 3.8	33.8 ± 8.0	36.2 ± 3.8	25.7 ± 2.0	16.5 ± 3.5*
hCG	Group I	60.3 ± 6.2	58.2 ± 5.5	60.3 ± 6.4	54.9 ± 7.0	49.4 ± 4.7	34.8 ± 3.8*
($mIU \cdot ml^{-1}$)	Group II	51.3 ± 13.6	49.4 ± 13.4	56.8 ± 1.6	53.1 ± 7.5	38.7 ± 9.2	26.4 ± 7.6*
ACTH	Group I	49.0 ± 9.5	35.7 ± 7.0	37.0 ± 8.2	28.0 ± 6.6	18.7 ± 8.2	22.8 ± 8.5
($pg \cdot ml^{-1}$)	Group II	54.0 ± 14.8	46.6 ± 19.6	26.4 ± 6.7	14.4 ± 2.1	15.0 ± 3.3	20.4 ± 2.2
Cortisol	Group I	18.7 ± 1.1	21.1 ± 1.1	15.8 ± 1.0	16.1 ± 3.3	13.6 ± 2.6	12.1 ± 1.6
($\mu g \cdot dl^{-1}$)	Group II	21.2 ± 1.3	21.8 ± 2.0	22.4 ± 2.9	10.6 ± 2.9	12.0 ± 2.6	14.2 ± 1.5

All values are mean ± SE and number of patients are seven for Group I and five for Group II.
*$P < 0.05$ compared with before induction.
†$P < 0.05$ compared with Group I.

sia. When the two groups were compared, Group I showed higher plasma P values than Group II in all samples after the induction of anaesthesia and plasma P level 24 hours after the induction of anaesthesia was significantly lower in Group II than in Group I. Plasma LH and hCG levels decreased gradually throughout the experimental period and no significant difference was observed between the two groups. Plasma ACTH and cortisol levels were higher before the induction of anaesthesia than 24 hours later but the differences were not significant in both groups. No significant secretory response was found during the procedure of oocyte pick-up and there were no significant differences in plasma ACTH and cortisol levels between the two groups. The occurrence of pregnancy was noted in one patient in Group I.

Discussion

From the endocrinological point of view, laparoscopic oocyte recovery under general anaesthesia has some disadvantages for successful IVF[1] and one of those is that hyperprolactinaemia during laparoscopy may cause luteal phase deficiency after oocyte pick-up. According to Lewin *et al.*,[4] one of the advantages of transvaginal ultrasound-guided oocyte pick-up over the laparoscopic technique is the lower plasma PRL levels during the operative procedures but the transvaginal approach has not been well characterized in this aspect. The present study showed that (1) considerable increases in plasma PRL levels and negligible changes in plasma ACTH and cortisol levels occurred during the transvaginal ultrasound-guided oocyte pick-up with the two types general anaesthesia, (2) the magnitude and duration of PRL response during the procedure were much greater in the neuroleptanaesthesia group than in the halothane group and (3) increase of plasma P level after oocyte pick-up was suppressed in Group II compared with Group I. Szalay *et al.* reported elevated levels of plasma PRL during laparoscopic oocyte recovery under neuroleptanaesthesia similar to our observations.[3] In their report, however, the elevated PRL level during laparoscopy was accompanied by high plasma cortisol levels ($> 70\ \mu g \cdot dl^{-1}$). It is well documented that surgical stress stimulates PRL, ACTH and cortisol secretion depending on the intensity and the duration of stress.[9,10] Therefore, the transvaginal approach under neuroleptanaesthesia in our study seemed less stressful than the laparoscopic approach, although only plasma PRL levels were increased.

In this study, we also observed relatively lower plasma P levels 24 hours after the induction of anaesthesia in Group II than those in Group I. In Group II, plasma PRL levels continued to be elevated for several hours far above $20\ ng \cdot ml^{-1}$ and, in an *in vitro* study,[11] those levels of PRL were high enough to inhibit P production in human granulosa cells. As there was no significant difference in the plasma LH and hCG levels between the two groups throughout the study, low plasma P levels observed in Group II possibly reflect the inhibition of P production by hyperprolactinaemia during and after the operative procedure. Absence of significant difference in the intraoperative changes of vital signs between the two groups suggested that droperidol and fentanyl used in neuroleptanaesthesia were responsible for the greater stimulation of prolactin secretion observed in Group II. It is known that droperidol increases PRL secretion by blockade of dopamine receptors in the brain and pituitary.[12] The

stimulatory effect of fentanyl on PRL secretion is also documented in human studies.[13] Since a transient low P level is potentially detrimental to uterine receptivity of embryo which is usually transferred within 72 hours after oocyte pick-up, we propose that droperidol and fentanyl be used carefully for anaesthesia for this procedure. Further studies are required, however, to draw the conclusion that halothane anaesthesia is more appropriate for IVF, since the number of patients and the rate of pregnancy were small in the present study.

In summary, higher plasma PRL levels and lower plasma P levels in the neuroleptanaesthesia group than in the halothane group were observed during and after transvaginal ultrasound-guided oocyte pick-up. Plasma ACTH and cortisol levels of the patients suggested that surgical stress was minimal in both groups. It is likely that droperidol and fentanyl, both used in neuroleptanaesthesia, were responsible for the hyperprolactinaemia which was a probable cause of low plasma P levels. These agents, therefore, should not be recommended as anaesthetic agents in the transvaginal ultrasound-guided oocyte pick-up.

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Résumé

Dans le cadre d'un programme de fertilisation in vitro, on a fait la cueillette d'ovules par voie transvaginale avec échographie chez 12 femmes infertiles. Pour ce faire, nous en avons anesthé siées sept avec de l'halothane et cinq par neuroleptanesthésie. En mesurant les niveaux plasmatiques pendant et après la procédure, nous avons trouvé plus de prolactine et moins de progestérone avec l'halothane qu'avec la neuroleptanesthésie. Les quantités d'ACTH et de cortisol plasmatiques, faibles dans les deux groupes, suggèrent un niveau minimal de stress chirurgical. Il est probable que le dropéridol et le fentanyl, utilisés dans le groupe neuroleptanesthésie, soient responsables d'une hyperprolactinémie suivie d'une inhibition de la sécrétion de progestérone et de ce fait, ils devraient être évités lors de la cueillette d'ovules.