ORIGINAL ARTICLE

Response of Ovary in Young Women Experiencing Laparoscopy under General Anaesthesia

W.P. Chow
A. Loganath
K.L. Peh
P.C.T. Chew
R. Gunasegaram
S.S. Ratnam

University Department of Obstetrics & Gynaecology, National University Hospital and Institute of Science & Forensic Medicine, Singapore

Summary

This study investigated whether changes in circulating levels of immunoreactive oestradiol-17β (E_2), progesterone (P) and testosterone (T) occur in women at follicular (n=18, age 25 to 39 years) and luteal (n=17, 25 to 39 years) phases of the normal menstrual cycles, experiencing laparoscopy after intravenous sedation with general anaesthesia. The pre- and intra-operative follicular phase plasma steroid hormone concentrations were 153.5±84.3 vs 297.4±220.8 pg/ml for E_2, 2.0±3.2 vs 3.3±3.8 ng/ml for P and 746.6±415.9 vs 1325.8±535.1 pg/ml for T, respectively. The corresponding luteal phase steroid levels were 259.7±120.2 vs 382.7±188.7 pg/ml, 7.0±4.8 vs 9.9±6.1 ng/ml and 819.4±355.7 vs 1703.5±1058.1 pg/ml. Using the Wilcoxon rank sum test, intra-operative hormone levels with the exception of P in the luteal phase were found to be significantly elevated ($p<0.05$). The results suggest that laparoscopy under general anaesthesia evokes increased secretion of ovarian hormones, possibly via the activation of hypothalamo-pituitary-ovarian axis.

Key words: Laparoscopy, general anaesthesia, endocrine changes, elevated oestradiol-17β, progesterone and testosterone levels, hypothalamo-pituitary-ovarian activation.

Introduction

Surgical procedures evoke profound endocrine and biochemical changes which result in increased substrate utilisation, a change in metabolism towards catabolism, negative nitrogen balance and retention of salt and water[1]. Intra-abdominal procedures are associated with much greater response than body surface surgery[2]. Cardiac surgery with cardio-pulmonary bypass induces profound metabolic changes[3]. Generally, the magnitude of the response is proportional to the severity of the operative trauma[4].

The evidence that neuroendocrine response to surgery is normally associated with marked increase in circulating concentrations of adrenocorticotrophic hormone (ACTH)[5], growth hormone (GH)[6], and prolactin (PRL)[7] seems to indicate activation of hypothalamo-pituitary axis as a possible mechanism for the increase. In this respect, previous studies have shown that surgical stress can influence the secretion of anterior pituitary hormones such as follicle-stimulating hormone (FSH), luteinising hormone (LH) and PRL intra-operatively in female patients[8]. This classic release may be expected to modulate ovarian function. However, data on E_2, P and T responses to surgery in women are limited. Because these hormones play a key role in female reproduction and because there is a possibility that hypertension and the endocrine disease itself could influence the course of anaesthesia and surgery, it could be beneficial for the safety of the patients if mechanisms involved in hormone release to surgery were elucidated. Specifically, the question whether a change in E_2, P and T secretion exists in women with infertility-related disorders undergoing laparoscopy under general anaesthesia has not been looked into. In the present study, we investigated the effect of anaesthetic and surgical stress due to laparoscopy on the levels of E_2, P and T before and at the end of the surgical procedure.

Material and Methods

Thirty-five women, scheduled for laparoscopic examination during the follicular (n=18, age 25 to 39 years) and luteal (n=17, age 25 to 39 years) phases of the normal menstrual cycle, gave informed consent to participate in this study. The stage of the cycle was determined by endometrial dating and plasma hormone levels. The laparoscopic procedure was performed on these women for investigation of subfertility. The pelvis was examined routinely without any ovarian manipulations, surgery or diathermy. Mild endometriosis was observed in 12 out of 18 patients in the follicular phase and in 11 out of 17 cases in the luteal phase. Women with pelvic inflammatory disease, polycystic ovaries and those on oral contraceptives were excluded from the study.

General anaesthesia was introduced in the usual manner. All the patients were anaesthetised under a similar regimen. Pre-anaesthetic medications were not used. A small intravenous dose of pethidine 0.5 mg/kg was administered just before induction of anaesthesia with thiopentone 4 to 5 mg/kg. Suxamethonium 1 to 1.5 mg/kg was used to facilitate tracheal intubation. Muscle relaxation was maintained with atracurium at the dosage of 0.4 mg/kg. Supplementary doses of atracurium were administered according to the clinical need of the patient. At the end of the laparoscopic procedure, residual neuromuscular blockage was antagonised with neostigmine and atropine.

Blood samples were taken by venepuncture 15 mins before surgery and at the end of the surgical procedure which lasted about 30 mins. Immediately after collection, blood samples were centrifuged at 1250 g at 4°C for 10 mins and the separated plasma was stored at -20°C until analysis.

The levels of E_2, P and T were measured by specific RIA according to WHO method (WHO Method Manual, 1990). The antisera for the respective steroids were donated by Primate Research Centre, Sukhoumi, USSR, S.B. Sufi, London, UK and B. Morris, Guildford, UK, under the auspices of the WHO. Two, 4, 6, 7, 16, 17-[^{3}H]E_2 (sp act 140-170 Ci/mmol), 1, 2, 6, 7, 16, 17-[^{3}H]P (sp act 100-130 Ci/mmol) and 1, 2, 6, 7-[^{3}H]T (sp act 80-105 Ci/mmol) were purchased from Amersham International Plc, UK. The unlabelled steroids were from Sigma Chemical Co, St Louis, MO, USA.

All assays were performed in duplicate and in a single batch. The assay sensitivity was 6.2 pg/ml for E_2, 15.6 pg/ml for P and 7.8 pg/ml for T. The mean intra- and inter-assay coefficients of variation were 4.5% and 6.2% for E_2, 5.7% and 7.3% for P and 5.0% and 9.0% for T, respectively. All samples were corrected for procedural losses during extraction. Recoveries of added E_2, P and T were 93.8%±3.9%, 88.4%±4.6% and 93.2%±3.9%, respectively.

The experimental results are expressed as mean±SD. It is important to note that in reviewing the data, each patient acts as her own control, that is to say, for each patient the pre-operative baseline level is the control for the intra-operative level which is the test. The significance of differences between the values of the pre- and intra-operative hormones was evaluated by the Wilcoxon rank sum test (two-tailed). Mean differences between the samples were considered to be significant at a p value of <0.05.

Results

Shown in Fig 1 are the pre- and intra-operative plasma E_2 levels of the 18 cases in the follicular phase. All patients responded to the stimulus of surgery with a prompt increase in E_2 levels. Intra-operatively, the E_2 concentrations (range 94.9-1060.2 pg/ml, mean±SD 297.4±220.8) were significantly elevated compared to the respective control values (range 50.2-325.6 pg/ml, mean±SD 153.5±84.3; P=0.0017). In all cases, the baseline pre-operative E_2 values were within the normal range of our women (range 43.5-153.0 pg/ml) at the follicular phase of the menstrual cycle. The overall intra-operative mean was 1.9-fold higher than that of the pre-anaesthetic mean. The single most impressive stimulation of E_2 was the 8.9-fold increase from 118.6 pg/ml to 1060.2 pg/ml.

The baseline and intra-operative plasma E_2 concentrations in the luteal phase of the 17 cases is illustrated in Fig 2. As in the follicular phase, the luteal phase E_2 levels during laparoscopy (range 167.4-704.7 pg/ml, mean±SD 382.7±188.7) were significantly elevated compared to the respective baseline values (range 78.1-533.3 pg/ml, mean±SD 259.7±120.2, P=0.0220). The pre-operative control values were within the normal range of our women (50-250 pg/ml) at the luteal phase in 10 out of the 17 patients. The intra-operative E_2 mean of this group was 1.5-fold higher than the basal mean.

Fig 3 illustrates significantly increased concentrations of follicular phase plasma P levels during surgery (range 1.1-17.5 ng/ml, mean±SD 3.3±3.8) compared to pre-anaesthetic values (range 0.62-14.4 ng/ml, mean±SD 2.0±3.2, P=0.0017). Seventeen out of 18 had pre- and intra-operative P levels within the normal range (<10 ng/ml) at the follicular phase of the menstrual cycle. The intra-operative P mean was 1.6-fold higher than the basal mean.

In contrast to the follicular phase, the luteal phase (Fig 4) intra-operative plasma P concentrations (range 1.7-15.7 ng/ml, mean±SD 9.9±6.1) were not significantly elevated compared to the respective control values (range 0.99-12.7 ng/ml, mean±SD 7.0±4.8, P=0.0761). Six out of the 17 women had pre-operative normal P values greater than 10 ng/ml (Fig 4). The intra-operative mean in this group was 1.4-fold higher than the control mean.

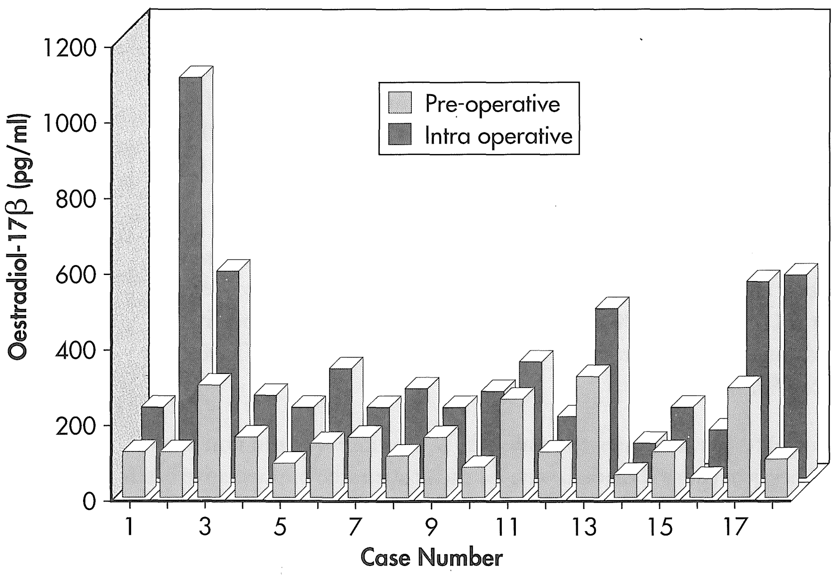

Fig 1: Pre- and intra-operative plasma oestradiol concentrations in the follicular phase of women (n=18), during laparoscopy under general anaesthesia (p=0.0017 Wilcoxon Rank Sum-test).

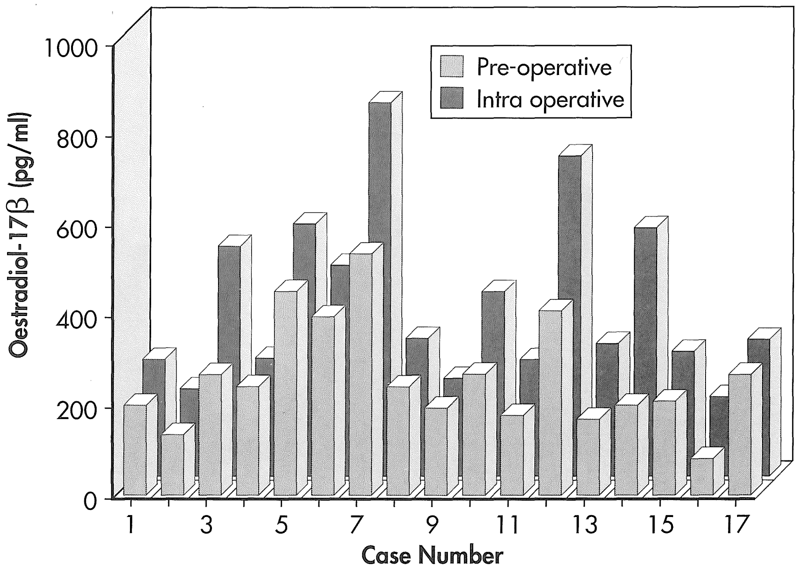

Fig 2: Pre- and intra-operative plasma oestradiol concentrations in the luteal phase of women (n=17), during laparoscopy under general anaesthesia (p=0.0219 Wilcoxon Rank Sum-test).

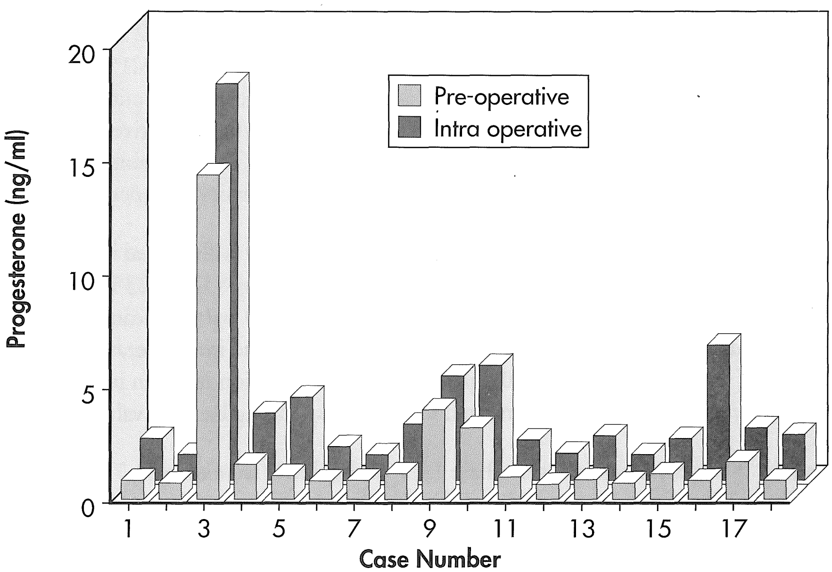

Fig 3: Pre- and intra-operative plasma progesterone concentrations in the follicular phase of women (n=18), during laparoscopy under general anaesthesia (p=0.0017 Wilcoxon Rank Sum-test).

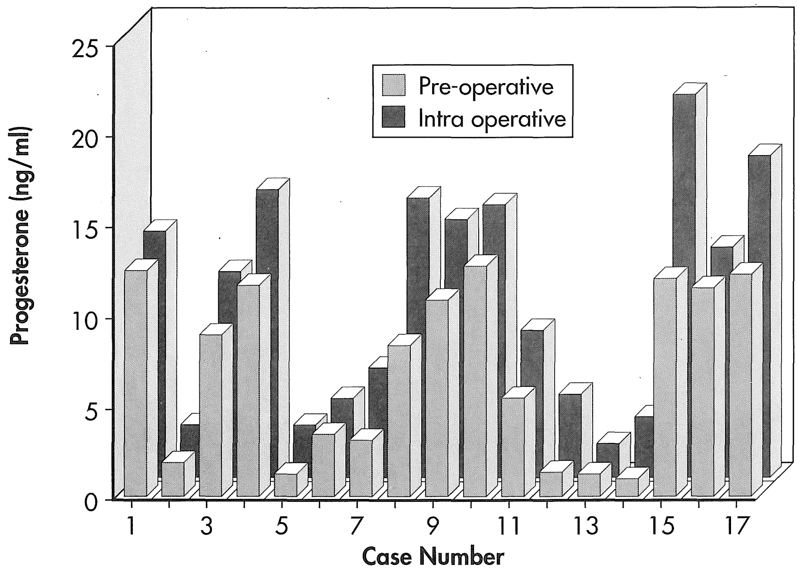

Fig 4: Pre- and intra-operative plasma progesterone concentrations in the luteal phase of women (n=17) during laparoscopy under general anaesthesia (p=0.0761 Wilcoxon Rank Sum-test).

The baseline and intra-operative follicular phase plasma T levels are depicted in Fig 5. During surgery, a prompt and marked elevation in T concentrations (range 459.6-2513.1 pg/ml, mean±SD 1325.8±535.1) compared to the pre-operative baseline levels (range 204.9-2094.2 pg/ml, mean±SD 746.6±415.9, P=0.0005) was observed in all patients. It is noteworthy that 14 patients had intra-operative T values outside the upper limit of normal range in our women (240-890 pg/ml, mean 590.0-±120.0).The intra-operative T level was 1.8-fold higher than that of the pre-anaesthetic mean. The highest absolute value of T was obtained in case no 15 that responded so dramatically to laparoscopy being 11.6-fold higher than the basal pre-operative level.

The pattern of T elevation in the luteal phase of women undergoing surgery is illustrated in Fig 6. It is evident that significantly increased plasma T concentrations during laparoscopy (range 837.7-5235.6 pg/ml, mean±SD 1703.5±1058.1) compared to pre-anaesthetic values (range 118.2-1466.0 pg/ml, mean±SD 819.4±355.7, P=0.0003) were observed in all the 17 women. Fifteen out of 17 patients had intra-operative plasma T values above the upper limit of normal range (240-890 pg/ml). A 2.1-fold elevation in mean intra-operative luteal phase T concentration was calculated when compared to the corresponding baseline values.

As might be expected, the mean baseline luteal phase E_2, P and T levels were raised 1.7-, 3.5- and 1.1-fold respectively when compared with the corresponding follicular phase levels. In a similar fashion, the mean luteal intra-operative plasma levels of the respective hormones were also elevated 1.3-, 3.0- and 1.3-fold.

The overall statistics of our data summarised in Table I, show that with the exception of plasma P in the luteal phase, marked and persistent elevations in intra-operative levels of the ovarian steroids occurred in both follicular and luteal phases of women during laparoscopy under general anaesthesia.

Table I
Summary of statistical data showing baseline and intra-operative hormone levels

Analyte	Follicular phase: Before anaesthesia	Follicular phase: During surgery under anaesthesia	Follicular phase: (P)	Luteal phase: Before anaesthesia	Luteal phase: During surgery under anaesthesia	Luteal phase: (P)
E_2-17β (pg/ml)	50.2-325.6	94.9-1060.2	0.0017	78.1-533.3	167.4-704.7	0.0220
Mean±SD	153.5±84.3	297.4±220.8		259.7±120.2	382.7±188.7	
P4 (ng/ml)	0.62-14.4	1.1-17.5	0.0017	0.99-12.8	1.7-15.7	0.0761
Mean±SD	2.0±3.2	3.3±3.8		7.0±4.8	9.9±6.1	
T (pg/ml)	204.9-2094.2	459.6-2513.1	0.0005	118.2-1466.0	837.7-5235.6	0.0003
Mean ±SD	746.6±415.9	1325.8±535.1		819.4±355.7	1703.5±1058.1	

Discussion

The question of whether surgery under general anaesthesia affects hypothalamo-pituitary-ovarian function has not been adequately answered. Earlier studies have reported conflicting results on endocrine changes in patients undergoing a variety of operations. A significant but transient drop of plasma E_2 during follicular phase and of plasma E_2 and P during the luteal phase following hysterectomy had been reported. But because no major fluctuations in FSH and LH levels were observed, the changes in steroid hormones were related to surgical manipulation in the ovarian region[9]. On the other hand, a significant intra-operative decrease in T, increase in cortisol (F) and LH together with variables in FSH levels from corresponding pre-operative levels in males undergoing pulmonary lobectomy might implicate a contribution from the anterior pituitary gland[10]. In contrast, an increased concentration in GH with no concomitant intra-operative change in concentrations of TSH, FSH and LH from control concentrations in a small group of men and pre- and post- menopausal women undergoing a variety of surgical procedures, namely: cholecystectomy, common duct exploration, hemigastrectomy and vasotomy, mastectomy, femoral nailing and bone grafting would imply a dichotomy in the response of the anterior pituitary to surgical stress[11]. It is a common finding that in most cases the serum concentrations following surgery gradually normalised to pre-surgical concentrations during the post-operative convalescent period[12]. Interestingly, another study in confirming the previous observation of decreased T and elevated serum LH levels in males who underwent pulmonary lobectomy, gastrectomy and cholecystectomy, found no significant increase in LH, FSH and T levels in menstruating females and post-menopausal women, both of whom underwent similar surgical procedures as men[13]. Surgical stress including general anaesthesia was suggested as the agent responsible for intra and post-operative changes in males and females. It is noteworthy, however, that the number of menstruating females studied was small and all had major non-gynaecological operations. In addition, controls in this study were patients without surgery and anaesthesia. The decline in intra-operative LH and peripheral ovarian steroids with an increase in PRL in a group of women of reproductive age undergoing a variety of operations, without compromise of ovarian vasculature (laparoscopy, laparotomy, lumbar laminectomy, fasciotomy of right arm and skin graft), compared to normal women, was attributed to direct inhibition of ovarian steroidogenesis by toxic effects of anaesthetic agents or to stress-induced changes[14]. The apparent paradox was resolved by the finding that in a group of pre-menopausal women who underwent hysterectomy for menorrhagia or ovarian cancer, increase in FSH, LH, PRL and cortisol in the general anaesthesia group as compared to epidural analgesia provided evidence of neurogenic blockade of anterior pituitary to surgical stress[15]. This study clearly implicated the hypothalamo-pituitary area as a site of action.

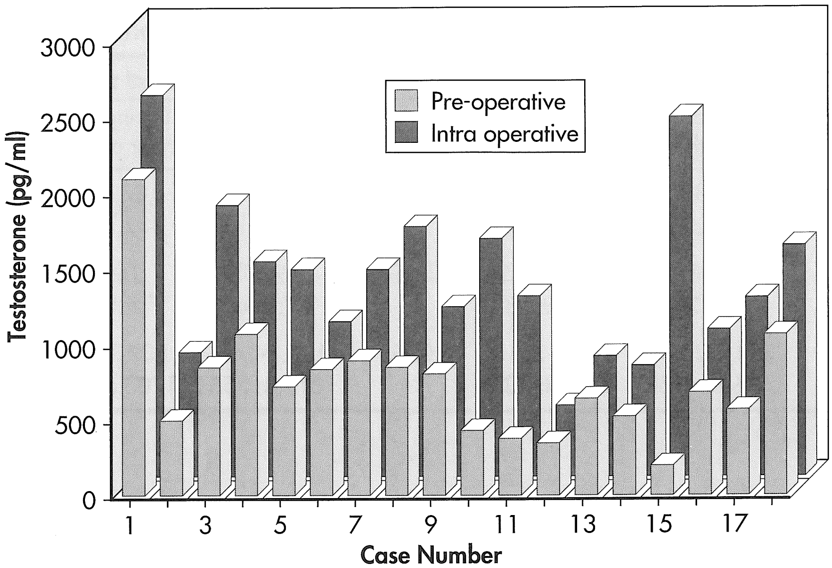

Fig 5: **Pre- and intra-operative plasma testosterone concentrations in the follicular phase of women (n=18) during laparoscopy under general anaesthesia (p=0.0006 Wilcoxon Rank Sum-test).**

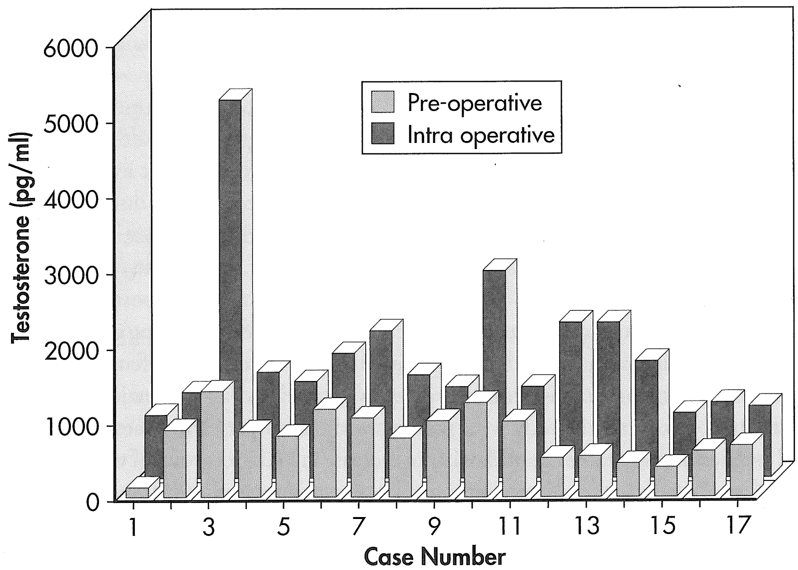

Fig 6: **Pre- and intra-operative plasma testosterone concentrations in the luteal phase of women (n=17) during laparoscopy under general anaesthesia (p=0.0003 Wilcoxon Rank Sum-test).**

In the light of these observations, the results of the current study are not inconsistent with the concept that surgical procedures involve hypothalamo-pituitary-gonadel axis that undoubtedly contributed to our findings. Indeed, our earlier studies have established increased activation of hypothalamo-pituitary function to laparoscopic stress[8]. This finding, taken together with our current observation, represents the first documented evidence for activation of hypothalamo-pituitary-ovarian axis in women of reproductive age experiencing laparoscopy under general anaesthesia. However, considerable additional experimental data will be required to place this in perspective. How long the hypothalamo-pituatary-ovarian drive persists during the period of recovery is, however, not established in this study. Whether the degree and duration of the intra-operative rise in steroid hormones correlates positively with the complexity of surgery warrants investigation. The mechanisms, the purpose and the necessity of the integrated endocrine-metabolic stress-response changes in man have yet to be clearly defined. It is possible that an altered hormonal environment is an evolutionary adaptation for survival under critical conditions.

Changes in reproductive hormones associated with operations may be of considerable clinical significance. Firstly, because both anterior pituitary and ovarian hormones are elevated during surgery, it is advisable not to do endometrial biopsy or hormone estimations after a woman has had an operation under general anaesthesia. How long the stimulation persists, is, however, not established in this study. There is evidence that in patients who underwent abdominal surgery, pre-operative changes in hypothalamo-pituatary-adrenal axis persisted for 72 hrs[16]. Therefore, evaluation of endocrine, metabolic and clinical chemistry tests on blood samples collected during or immediately after surgery cannot provide an accurate basis in clinical practice.

Secondly, our findings offer a probable explanation for the common and unsolved problem in assisted techniques of reproduction, that is, implantation failure. Increased P level can lead to a disparity between embryological and endometrial events that impair implantation. Further studies in this area are required to determine at what steroid hormone levels the timing of embryo transfer can be synchronised with endometrial development, for successful implantation to occur.

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