pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20262088

Original Research Article

Post-operative hyperglycaemia in non-diabetic patients following elective gynaecological surgeries: incidence and risk factors

Piyush Vohra[1], Rimpi Singla[1]*, Minakshi Rohilla[1], Sukant Garg[2], Sanjay Bhadada[3], Indu Verma[4], Neelam Aggarwal[1]

[1]Department of Obstetrics and Gynaecology, Post Graduate Institute of Medical Education and Research, Chandigarh, India
[2]Department of Pathology, HSJ Institute of Dental Sciences, Chandigarh, India
[3]Department of Endocrinology, Post Graduate Institute of Medical Education and Research, Chandigarh, India
[4]Department of Biochemistry, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Received: 17 December 2024
Revised: 28 May 2026
Accepted: 01 June 2026

***Correspondence:**
Dr. Rimpi Singla,
E-mail: drrimpisingla@gmail.com

ABSTRACT

Background: There is a dearth of information on the incidence, risk factors, and impact of postoperative hyperglycemia following Gynaecological surgeries. This study explores the incidence and predictors of postoperative hyperglycemia following elective Gynaecological surgeries and its association with postoperative outcomes.
Methods: The non-diabetic patients admitted for elective gynaecological surgeries who met inclusion criteria and were willing to participate were enrolled. Blood glucose was checked in the post-operative period at 2,6,12,24, and 48 hours, respectively. Hyperglycemia was defined as any blood glucose value of $\geq$126 mg/dl and clinically significant hyperglycemia as $\geq$180 mg/dl. All patients were followed up for 30 days. Outcome measures were the incidence of post-operative hyperglycemia and the relation of hyperglycemia with peri-operative parameters and infections.
Results: Out of the 200 patients, post-operative hyperglycaemia was observed in 61.5% of patients and 12.5% had severe hyperglycaemia. The mean BMI of patients with hyperglycaemia (25.8±3.8kg/m^2) was significantly more than euglycemic ones (24.4±4.0kg/m^2 (p=0.019)). Procedures lasting >2 hours were significantly associated with hyperglycemia (p=0.002) and its severity (p=0.006). Post-operative infectious complications and the need for therapeutic antibiotics were higher among hyperglycaemic patients (p=0.053).
Conclusions: Postoperative hyperglycemia in non-diabetic patients following elective gynaecologic surgeries is associated with an increased risk of infections. Postoperative monitoring of blood glucose should be done for all patients. If universal monitoring is not feasible, then patients with high BMI undergoing open abdominal surgeries lasting more than 2 hours should undergo vigilant post-operative monitoring for hyperglycemia.

Keywords: Postoperative, Hyperglycemia, Elective gynaecological surgeries, Non- diabetic

INTRODUCTION

Acute post-operative hyperglycemia has been found to be associated with an increased risk of postoperative complications.[1-3] Most of our knowledge on post-operative hyperglycemia and its implications is based on retrospective studies conducted in cardiac, neurosurgery, hepatobiliary-pancreatic, colorectal and general surgery and critically ill patient cohorts.[2-8] In most of the previous studies, gynaecological patients had been a fraction of the larger surgical cohort comprising various specialties. Perioperative hyperglycemia is a response to stress and inflammation which might be influenced by the duration and invasiveness of surgery and pre-existing medical co-morbidities.[9,10] The risk profile of patients undergoing elective gynaecological surgeries is different from others. Gynaecological elective surgeries mostly involve class 1 (clean) or class 2 (clean-contaminated) wounds and hence, different from general surgery or trauma patients.[11] Further, patients undergoing emergency surgeries are at higher risk for adverse outcomes. So, the incidence of hyperglycemia and its effects as derived from pooled data from other surgical specialties and situations may not be representative of the same among patients undergoing elective gynaecologic procedures. There are hardly any studies that have objectively looked at risk factors for hyperglycemia. Considering these lacunae in existing knowledge, we planned to undertake a prospective investigation to estimate the incidence of postoperative hyperglycemia following elective gynaecological surgeries and to find its risk factors to identify those patients who are at high risk of developing post-operative hyperglycemia.

METHODS

Study design and settings

This prospective cohort study was carried out in the Department of Obstetrics and Gynaecology, Post Graduate Institute of Medical Education and Research from from June 2018 to June 2019. Study was initiated after being approved by the Institute's Ethics Committee (Reference: NK/4221/MD/1587-88) and was carried out in compliance with principles set forth in Helsinki Declaration (revised in 2013).

Participants

Consecutive patients admitted for elective gynaecological Surgeries with an expected post-operative hospital stay of at least 48 hours were explained about and invited to participate in the study. Patients with pre-existing diabetes, any infectious co-morbidity, severe anaemia, using medications that would affect glucose metabolism (beta blockers, thiazides, corticosteroids, etc.), and not willing to participate in the study were excluded. Patients who met inclusion criteria were recruited after obtaining written informed consent. With 40% average incidence and 7% marginal error with a 95% confidence interval, the required sample size was 190.

Methods

Baseline demographic and clinical data and details of planned surgery were recorded on pre-designed proforma. Body Mass Index (BMI) was calculated, and the American Society of Anaesthesiologists (ASA) physical status was assessed. Patients underwent pre-operative preparation and were delivered prophylactic antibiotics as per the department's protocol (single dose of cefazolin 2 gm). Intra-operative details such as anaesthesia, surgical approach, incision, the actual procedure, and duration of surgery were recorded. Blood glucose was monitored in post-operative period at 2,6,12,24, and 48 hours using the Fingerstick method. Caution was exercised to ensure that the patient had not received dextrose infusion within at least two hours before glucose was tested. Patients were orally allowed as per operating surgeon's discretion.

Diagnostic criteria

Based on the highest recorded glucose value, patients were classified as normoglycemic (all blood glucose values of <126 mg/dl), mildly hyperglycaemic (any blood glucose values ≥126 and <180 mg/dl), and clinically significant hyperglycaemic (any blood glucose value ≥180mg/dl).[12,13]

Patients who had hyperglycemia underwent stringent blood glucose monitoring. Patients with blood glucose of more than 180mg/dl received regular insulin by sliding scale, in consultation with the endocrinologist. Their HbA1c levels were also checked.

Baseline data and relevant operative details of patients with hyperglycemia were compared with euglycemic patients to identify the factors associated with hyperglycemia. All the patients were followed up for 30 days for post-operative infections, especially surgical site infection. The incidence of infections was compared between the two groups. Outcome measures were the incidence of post-operative hyperglycemia, the relation between hyperglycemia, and pre-operative and intra-operative parameters. The incidence of adverse outcomes among patients manifesting post-operative hyperglycemia was compared to normoglycemic patients.

Statistical analysis

Descriptive analysis was done for all variables to see the distributions of categorical variables and mean values for continuous variables. For comparisons of measurable data for two groups, Student t test or Mann-Whitney U test was used depending upon its normality/skewness.

For comparisons of measurable data for more than two groups, analysis of variance (for normal distribution) or the Kruskal-Wallis test for non-normally distributed parameters was applied. To find the association of categorical/classified data and nominal data with the groups, the $\chi 2$ test or the Fisher exact test whichever is applicable was used. P value of <0.05 was considered significant.

RESULTS

Participants

We assessed 268 patients for eligibility. After excluding 68 patients (figure 1) due to co-morbidities, short expected post-operative stay, or not willing to participate, we enrolled 200 patients. Any patient who had any complication after discharge reported to the hospital and others were contacted personally or telephonically. Hence, none of the patients was lost to follow-up.

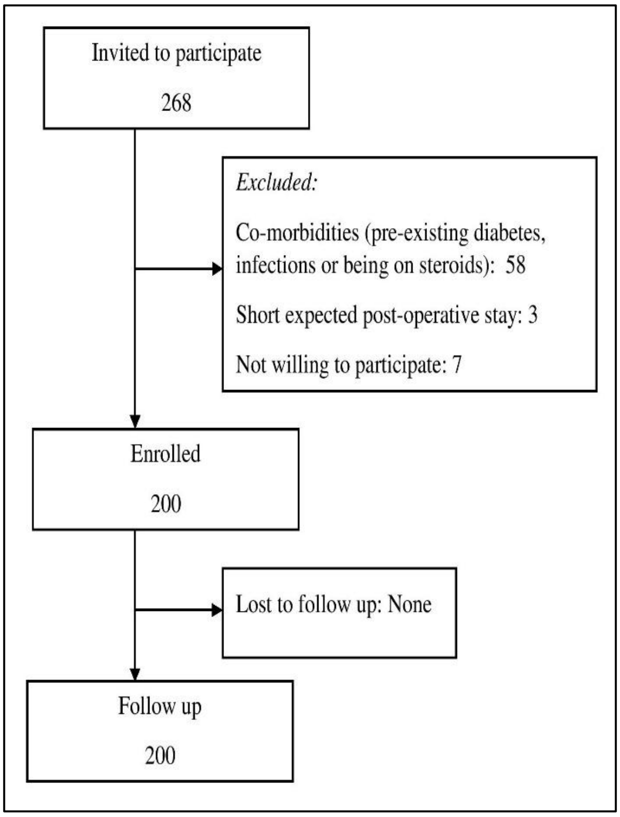

Figure 1: Study flow chart.

Descriptive Data

Demographic details and baseline clinical data

Sixteen patients had received neo-adjuvant chemotherapy, but their pre-operative blood counts were in the normal range. Most of the hypertensive patients had well-controlled blood pressure (BP). Maximum systolic blood pressure was 150 mm Hg and maximum diastolic BP was 90 mm Hg. All the patients had ASA 1 or 2 status. Pre-operative investigations including blood glucose values were within normal range (Table 1).

Operative details

Most of the patients were operated for ovarian cancer (30%) and abnormal uterine bleeding (AUB) (30%). Other indications included benign ovarian tumours, carcinoma endometrium, uterine or vault prolapse, uterine fibroids, rectovaginal fistulas, carcinoma cervix and pre-invasive lesions of cervix, Mullerian anomalies, etc.

Most of the patients (87%) received general anaesthesia with or without epidural analgesia (Table 1). Fifty-six percent of all patients required low molecular weight heparin for pharmacological prophylaxis against deep vein thrombosis.

Adverse events

Ten patients (5% of all) had Surgical Site Infection (SSI). Eight patients suffered from Urinary Tract Infection (UTI) and four patients developed Lower Respiratory Tract Infections. Therapeutic antibiotics were given to 21 patients, i.e., 10.5% of the total patients.

Table 1: Baseline clinical and laboratory data and operative details.

Parameters	Value
Age (mean±SD) (years)	44.16±13.13
BMI (mean±SD) kg/m^2	25.29±3.97
ASA physical status 1, N (%)	117 (58.5)
ASA physical status 2, N (%)	83 (41.5)
Baseline investigations (mean±SD)	
FBS (mg/dl)	87.01±7.47
PPBS (mg/dl)	110.77±13.41
Hb (g/dl)	11.18±1.54
Creatinine (mg/dl)	0.77±0.16
TSH (µIU/ml)	2.45±1.48
Operative details N (%)	
Anaesthesia	
Spinal anaesthesia	26 (13.0)
General anaesthesia	87 (43.5)
General+epidural anaesthesia	87 (43.5)
Surgical approach	
Abdominal- midline vertical	110 (55.0)
Abdominal-Pfannenstiel	30 (15.0)
Minimal invasive[a]	33 (16.5)
Vaginal	27 (13.5)

BMI: Body mass index, ASA: American society of anaesthesiologists, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, Hb: Haemoglobin, TSH: Thyroid stimulating hormone;
[a]minimal invasive surgery including laparoscopic, hysteroscopic, and robotic surgeries.

Outcome details

Hyperglycaemia

Out of 200 patients, 123 (61.5%) patients had post-operative hyperglycaemia while 12.5% suffered clinically significant hyperglycaemia.

Sixty-two patients (over 50% of hyperglycaemic patients) had first high glucose value at two hrs. of surgery and 27% of hyperglycaemic patients experienced first high glucose value at the end of 6th postoperative hour, approximately 15% at 12 hours, 7% at 24 hours, 2% at 48 hours after surgery.

Comparison of baseline data between euglycemic and hyperglycaemic patients

There was no difference in age and place of residence of the patients with and without hyperglycemia (Table 2). As we observe hyperglycemia across various slabs of BMI classification (Table 2), larger proportion of hyperglycaemic patients had higher BMI as compared to normoglycemic patients. The mean BMI of patients with hyperglycemia (25.8±3.8 kg/m^2) was significantly more than that of patients without hyperglycemia (24.4±4.0 kg/m^2 (p=0.019). Further, the mean BMI (26.99±3.68 kg/m^2) of patients with significant hyperglycemia (>180 mg/dl) was significantly higher than mildly hyperglycaemic patients (25.5±3.8 kg/m^2) (p=0.016). Higher proportion of patients (69%) with ASA 2 status as compared to patients with ASA 1 status (56%) had hyperglycemia but the difference was not significant.

Table 2: Comparison of baseline data of hyperglycaemic and euglycemic patients.

Parameters	Hyperglycemia	Euglycemia	P value
Age (mean±SD) (years)	45.0±12.11	42.7±14.5	0.229
Residence			
Rural N (%)	84 (59.6)	57 (40.4)	0.387
Urban N (%)	39 (66.1)	20 (33.9)	
Hypertension N (%)	26 (63.4)	15 (36.6)	0.778
SBP (mean±SD) mm Hg	117±11.7	115±12	0.338
DBP (mean±SD) mm Hg	75±7.6	74±8	0.373
BMI N (%)			
18.5 or less (underweight)	3 (2.4)	3 (3.9)	0.612
18.5-24.99 (normal weight)	50 (40.7)	37 (48.1)	
25-29.99 (overweight)	55 (44.7)	32 (41.6)	
30-34.99 (obesity class 1)	13 (10.6)	4 (5.2)	
35-39.99 (obesity class 2)	2 (1.6)	1 (1.3)	
ASA physical status N (%)			
ASA physical status 1	66 (56.4)	51 (43.6)	0.079
ASA physical status 2	57 (68.7)	26 (31.3)	

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; ASA: American society of anaesthesiologists.

Table 3: Comparison of operative details of hyperglycaemic and euglycemic patients.

Parameters	Euglycemia	Hyperglycemia	P value
Surgical approach N (%)			
Abdominal-midline vertical (n=110)	32 (29.1)	78 (70.9)	0.029
Abdominal-Pfannenstiel (n=30)	16 (53.3)	14 (46.7)	
Minimal invasive surgery (n=33)[a]	16 (48.5)	17 (51.5)	
Vaginal (n=27)	13 (48.14)	14 (51.85)	
Anaesthesia N (%)			
Spinal anaesthesia (n=26)	13 (50)	13 (50)	0.129
General+epidural anaesthesia (n=174)	64 (36.8)	110 (63.2)	
Duration of surgery N (%)			
Less than 2 h (n=60)	33 (55)	27 (45)	0.002
More than 2 h (n=140)	44 (31.4)	96 (68.6)	
Duration of surgery (mean±SD) minutes	117.08±52.99	131.75±45.44	0.038

[a] Minimal invasive surgery including laparoscopic, hysteroscopic and robotic surgeries.

Table 4: Relationship of postoperative adverse outcomes with hyperglycemia.

	Euglycemia (n=77)	Hyperglycemia (n=123)	Mild hyperglycemia (126-179 mg/dl)	Severe hyperglycemia (>180 mg/dl)
SSI				
Grade 1	2 (2.6%)	6 (4.9%)	6 (6.1%)	0
Grade 3	1 (1.3%)	1 (0.8%)	0	1 (4%)
P value	0.690		0.089	
UTI	0	8 (6.5%)	5 (5.1%)	3 (12%)
P value	0.022		0.021	

SSI: Surgical site infection, UTI: Urinary tract infection; Relation of intra-operative factors with hyperglycemia

As we compared various approaches to surgery, the abdominal route through midline vertical incision was associated with a significantly higher incidence of hyperglycemia as compared to other approaches (p=0.029); 72% of patients with clinically significant hyperglycemia versus 61% of mildly hyperglycaemic ones had midline vertical incision (p=0.132) (Table 3).

Duration of surgery was related to the occurrence of and severity of hyperglycemia (Table 3). Eighty-four percent of significantly hyperglycaemic patients as compared to 76.5% of mildly hyperglycaemic patients had duration of surgery >2 hours; p=0.006). As per the classification table of Logistic Regression by Enter Method, it was found that parameters such as BMI, route of surgery (abdominal, vaginal, or minimally invasive), type of incision (midline vertical abdominal, Pfannenstiel, or laparoscopy), and duration of surgery taken together would predict the presence of hyperglycemia with sensitivity 86.2% but its specificity was only 46.8%. In Forward Step-wise (Conditional) Logistic Regression, the duration of surgery of less than two hours alone (which tends to negate the presence of the hyperglycemia) predicts hyperglycemia with a sensitivity of 78.0% and specificity of 42.9% and overall predicted correct 64.5%. Post-operative infectious complications (SSI and UTI), and the need for therapeutic antibiotics were higher among hyperglycaemic patients as compared to euglycemic patients. Urinary tract infection was significantly associated with hyperglycemia and its severity (p=0.021).

DISCUSSION

The incidence of postoperative hyperglycaemia varies across different studies due to the heterogeneity of defining criteria and study populations. Having defined hyperglycemia as any blood glucose value of more than 126 mg/dl, we found the incidence of post-operative hyperglycemia to be 61.5% which is similar to previously reported incidence (55-66%) among non-gynaecological surgical cohorts that have used similar criteria to define hyperglycemia.[12,13] As the cut-off value for definition increases, the incidence of hyperglycemia decreases. It has been found to be 46% at a cut-off of 140 mg/dl and 10.6% to 17.2% when hyperglycemia was defined as a blood glucose value of ≥180 mg/dl.[2,14,15] In our study also, 12.5% of patients had a blood glucose value of ≥180 mg/dl.

Monitoring for hyperglycemia following elective gynaecological procedures is important as it was found to be associated with infectious morbidity. Out of individual parameters of infectious complications, urinary tract infections were significantly higher among patients with hyperglycemia. The majority of the patients (seven out of ten) with SSI had hyperglycemia. Though this was not statistically significant, it cannot be ignored. Similarly, in a recent study of 2447 non-diabetic patients who underwent colorectal surgeries, post-operative hyperglycemia was associated with higher rates of sepsis (3.5% vs 0.61%) and reoperations (7.3% vs 3.1%, P=0.006).[12] Talbot et al found a higher rate of SSI (3.7% vs 0.6%) with postoperative blood glucose of >250 mg/dl as compared to blood glucose of <150 mg/dl.[16] Postoperative hyperglycemia (>140 mg/dl) has been shown to be the strongest independent predictor of SSI.[7] Incidence of adverse outcomes has been found to have a direct correlation with severity of hyperglycemia also (63.6, 30.6, and 13 % for severe hyperglycemia, mild hyperglycemia and normoglycemia respectively, p<0.001) in non-diabetic patients.[13] There was no significant association of infections with the severity of hyperglycemia, maybe because of timely treatment with insulin or due to small numbers. Patients with blood glucose of >180mg/dl were treated with insulin. With this target as in NICE-SUGAR trial, none of our patients experienced hypoglycaemia.[17] The majority of the hyperglycaemic patients (50%) had first episode of hyperglycaemia after two hours of surgery, 27% at six hours of surgery. Very few patients were diagnosed to have hyperglycaemia at 12 and 24 hours. As a large proportion of patients manifested hyperglycaemia at two hours of surgery, it is inferred that hyperglycaemia may have occurred earlier than this or even intra-operatively. Thus, intra-operative monitoring of glucose may be considered in non-diabetic patients also to prevent post-operative infections.

Out of all the possible pre-operative risk factors, BMI showed a significant association not only with the occurrence of hyperglycemia but also its severity. Patients with higher BMI may be harbouring underlying insulin resistance unmasked by surgical stress. Thus, non-diabetic obese patients should receive vigilant post-operative blood glucose monitoring. As we compared the different intra-operative parameters, a greater number of women who underwent open abdominal surgeries manifested hyperglycemia. The incidence of hyperglycemia was higher when duration of the procedure was more than two hours. All these factors (high BMI, type of incision, actual surgical procedure, duration of surgery) taken together would predict the occurrence of hyperglycemia with 86.2% sensitivity but its specificity was only 46.8%.

Duration of surgery of less than two hours tends to negate the occurrence of hyperglycemia. Previous investigations have pointed out that the risk of postoperative adverse events is related to stress-induced hyperglycemia rather than pre-existing diabetes.[2,9,10] Surgical stress affects the finely tuned balance between hepatic glucose production and its peripheral utilization. The stress response triggers a cascade of endocrine responses through activation of the hypothalamo-pituitary-adrenal axis resulting in an increase in catecholamines, which further leads to an increase in peripheral insulin resistance.[18] Higher rate of complications among non-diabetic patients having post-operative hyperglycemia may be due to an extreme inflammatory response.[19] In the current study also, intra-operative factors like open abdominal approach to surgery (over minimal invasive route) and prolonged duration of surgery were significantly associated with hyperglycemia.

Hyperglycemia may lead to abnormal function of monocytes and neutrophils, decreased intracellular bactericidal activity, and overproduction of reactive oxygen and hence, an increased risk of infections.[20] Thus, diagnosis of post-operative hyperglycemia indirectly warrants increased vigilance for post-operative infections.

Strengths

This was a prospective investigation to identify the incidence of post-operative hyperglycemia exclusively following elective gynaecologic surgeries among non-diabetic patients. Complete follow-up of all the patients with zero attrition provides complete data on 30-day postoperative period. Through this study, we looked at all the possible factors associated with increased risk of hyperglycemia so that if not all, at least the patients having the identified risk factors should be subjected to post-op glucose monitoring.

Limitations

A larger sample size may have resulted in clear differences in various parameters where the difference is observed but had not reached statistical significance. Results could have been confidently generalized with a larger sample size. Since most of the hyperglycaemic patients had their first high blood glucose value recorded two hours post-op, there is a high chance that many patients may have had hyperglycemia during surgery.

CONCLUSION

In conclusion, postoperative hyperglycemia following elective gynaecological surgeries is associated with increased infectious morbidity in non-diabetic patients. Hence, all patients undergoing elective gynaecological surgeries should also be monitored for post-operative hyperglycemia. Considering the occurrence of hyperglycemia in the majority of patients within two hours of surgery, intra-operative glucose monitoring may also be considered in non-diabetic patients. If universal monitoring is not feasible, then patients with high BMI undergoing open abdominal surgeries lasting more than two hours should be subjected to vigilant monitoring for hyperglycemia in the postoperative period.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee (NK/4221/MD/1587-88)

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Cite this article as: Vohra P, Singla R, Rohilla M, Garg S, Bhadada S, Verma I, et al. Post-operative hyperglycaemia in non-diabetic patients following elective gynaecological surgeries: incidence and risk factors. Int J Reprod Contracept Obstet Gynecol 2026;15:2465-71.