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ORIGINAL RESEARCH

Absolute Iron-Deficiency Anaemia, Intravenous Iron Replacement and Depression Prevalence in Pre-Operative Planned Gynecology Surgery: A Pre-Post Intervention Study

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Abstract

Background: Iron-deficiency anaemia is common amongst women awaiting gynaecological surgery and often co-exists with and is a risk factor for depression and anxiety. As part of our pre-operative optimisation, we commonly treat specific cases of iron-deficiency anaemia with intravenous iron. Our objective was to study the relationship between iron-deficiency anaemia, intravenous iron correction, and the prevalence of depression and anxiety in our population.

Methods: We designed a prospective pre-post intervention questionnaire-based study that was carried out at Homerton Healthcare NHS Foundation Trust. The population included 82 non-pregnant, adult patients awaiting elective gynaecological surgery with laboratory findings consistent with absolute iron-deficiency anaemia. Baseline information was collated, and depression and anxiety scores were collected pre- and post-intravenous iron replenishment.

Results: The prevalence of depression and anxiety reduced significantly following iron replacement (33% vs. 10%, $p < 0.001$, and 18% vs. 5%, $p < 0.001$ respectively). There was a significant downgrade of depression category from pre- to post-intervention, $p < 0.001$. Additionally, participants who were initially more severely anaemic had a lower prevalence of post-intervention depression compared with those with mild-moderate anaemia (2% vs. 18%, $p < 0.019$).

Conclusions: These results suggest that effective correction of iron-deficiency anaemia in pre-operative gynecological surgery patients could lead to improvements in mental health outcomes ahead of planned surgery. This study highlights the potential impact of iron-deficiency anaemia correction on pre-operative mood disorders, which are linked to surgical outcomes, patient experiences, and overall satisfaction. Further research is needed to explore the broader implications of this relationship.

Keywords

Iron-deficiency anaemia, Depression, Gynecology, Intravenous iron

Introduction

Anaemia is defined by the World Health Organisation as haemoglobin (Hb) concentration of less than 120 $g.l^{-1}$ in women [1], with a ferritin concentration of less than 15 $\mu g.l^{-1}$ indicating absolute iron deficiency [2]. Iron-deficiency anaemia (IDA) is common in women awaiting gynaecological surgery [3]. Correction of IDA, in the form of oral iron supplementation or intravenous iron infusion, is recommended prior to elective surgery to improve perioperative outcomes [4]. To assess the efficacy of this intervention, most studies focus on

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primary perioperative outcomes such as donor red cell transfusion or mortality [5]. To date, the effect of correcting IDA on the symptom burden of mental health for patients ahead of surgery has not been explored.

Previously at our institution, we followed-up pre-operative patients after intravenous iron replacement to learn more about the effects of iron correction on the patient experience. We demonstrated exceedingly high patient satisfaction scores, as well as positive verbatim responses, suggestive of an improvement in pre-operative mental health [6].

Anaemia is associated with mental health conditions, including depression and anxiety [7-10]. In addition, IDA has specifically been associated with an increased incidence of both depression and anxiety, and when corrected, this risk is reduced [10]. For perioperative patients, severe mental illness is associated with increased post-operative morbidity [11] including poor wound healing, more severe post-operative pain, and increased mortality [12].

Depression and anxiety are common conditions, affecting 16% of adults in the UK [13]. Although the importance of addressing such psychological needs before surgery is widely acknowledged, the most effective method for handling these issues of prehabilitation and optimisation remains unknown [14]. It is essential to address any potential organic factors contributing to poor mental health. Therefore, alongside treating the surgical condition, all possible factors should be considered, including iron replacement for IDA, with the goal of enhancing surgical outcomes.

Objectives

We sought to ascertain if there is a relationship between correction of IDA using intravenous iron in patients awaiting planned gynecological surgery and the prevalence of depression. Secondary objectives included exploring the same relationship with regards to the prevalence of anxiety, the effectiveness of intravenous iron replacement for IDA, and the prevalence of depression and anxiety in pre-operative gynecological surgery patients. We hypothesized that by correcting pre-operative IDA in women awaiting planned gynecological surgery, we would reduce the prevalence of depression and anxiety symptoms at a later stage in the pre-operative pathway.

Methods

We conducted a prospective pre-post intervention study, where depression scores were compared pre- and post-correction of IDA with intravenous iron in women awaiting gynaecological surgery. This was a single-centre study enrolling patients at our institution, Homerton Healthcare NHS Foundation Trust, London, United Kingdom.

Inclusion criteria were: Women aged between 18-59 years; awaiting planned gynaecological surgery; diagnosis of pre-operative absolute IDA based on our local laboratory thresholds (Hb < 120 $g.l^{-1}$ and ferritin < 30 $\mu g.l^{-1}$ and iron saturations < 20%); planned for intravenous iron replenishment as per our institution's local policy (indications include: severe IDA, failure of oral iron replacement, intolerance of oral iron, major surgery planned, major blood loss expected); at least 4-weeks until planned surgery. Exclusion criteria included pregnant patients, patient refusal of intravenous iron, and patient refusal of consent to the study or no research recruiter available. All patients who met the inclusion criteria were invited to participate in the study. They were approached on the day of their planned iron infusion by a member of the research team and were provided with written information on the study. Following agreement of participation, informed written consent was gained.

Baseline demographic information including age and weight were collected. The pre-operative assessment form and electronic patient record provided details of their co-morbidities, ASA score, current medications, allergies, planned surgery, and recent laboratory tests (Hb, ferritin, iron saturations). Participants were then asked to complete two written questionnaires to score their depression and anxiety levels: 1) Patient Health Questionnaire-9 (PHQ-9) [15], a 9-question tool with 0-3 points per question, 2) Generalised Anxiety Disorder-7 (GAD-7) [16], a 7-question tool with 0-3 points per question (Appendix 1). These tools have been used clinically to screen, diagnose, assess and monitor disease severity and are validated for use in research [15,16].

All pre-intervention data and assessments were collected before participants received their planned intervention of intravenous iron (ferric carboxymaltose, Ferinject® Vifor Pharma, Zurich Switzerland). The total dosing for the ferric carboxymaltose iron requirement was based on actual weight and Hb, as per the manufacturer's guidance (Appendix 2). If the total dose exceeded the maximum dose within a single encounter (20 $mg.kg^{-1}$ up to 1000 mg), the remainder of the dose was administered seven days later.

Four to six weeks after the intervention, PHQ-9 and GAD-7 questionnaires were repeated via a telephone call. Participants were also asked if, since their intervention, they had been newly diagnosed with depression or anxiety and whether they had commenced new medications for either. Within 48-hours of the post-intervention questionnaires, laboratory tests were conducted including Hb, ferritin and iron saturations.

Participants who scored in the moderately severe or severe category on PHQ-9, or in the severe category on GAD-7, or who displayed suicidal ideation on either the pre- or post-intervention questionnaire, were informed of these findings and formally advised to

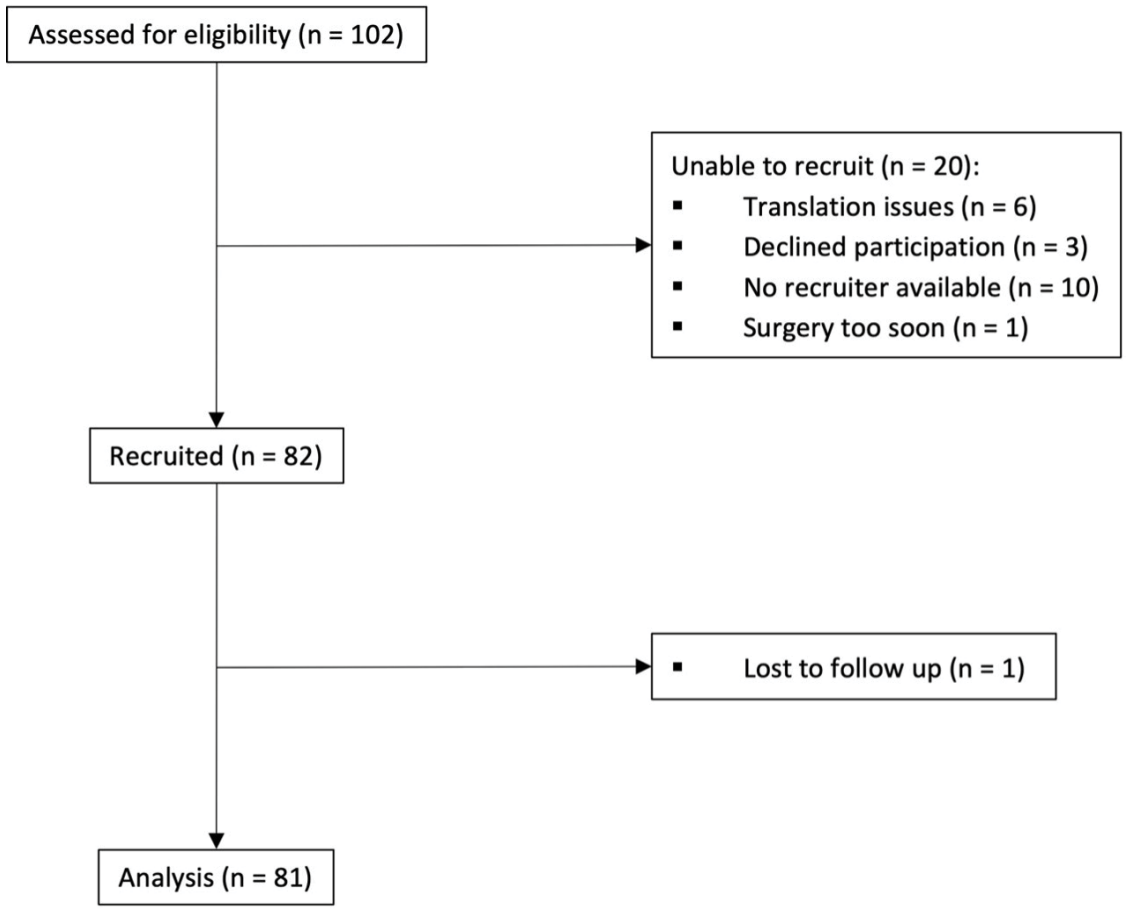

Figure 1: Patient flow diagram.

make an appointment with their primary care physician for further evaluation. Where consent was given, we also communicated the questionnaire results to their primary care physician.

All data were entered into an electronic database and anonymised. Required sample size was based on an estimated baseline prevalence of depression in our target population of 25% [13,17-20]. A power calculation was carried out prior to commencement of the study, which indicated 81 participants would be required to detect a 50% reduction in depression following the intervention. The software IBM SPSS Statistics for Windows (version 28) was used to analyse the data. The statistical methods used included Paired-samples t-tests, Wilcoxon Signed-Rank tests and Chi-Square tests.

Results

Between February 2021 and March 2022 there were 102 eligible participants, of which 82 participants consented and underwent the intervention. One participant was lost to follow-up, and 81 participants successfully completed the study (Figure 1). Baseline demographics, planned surgery, and medical history are shown in Table 1.

Administration of intravenous iron resulted in a significant correction of anaemia, with a mean Hb increase from pre-intervention (97 $g.l^{-1}$) to post-intervention (120 $g.l^{-1}$) of 23 $g.l^{-1}$, $p < 0.001$. Ferritin and iron saturations also increased significantly post-intervention, with mean increments of 258 $\mu g.l^{-1}$ and 15.6% respectively, $p < 0.001$ for both (Table 2).

Pre- and post-intervention PHQ-9 scores were 7.68 and 3.72 respectively, mean difference 3.96, $p < 0.001$ (Table 3). Depression was defined as a PHQ-9 score of more than or equal to 10. The pre-intervention prevalence of depression was 33% and showed a significant reduction post-intervention at 10%, $p < 0.001$ (Table 4). There was no difference in the pre-intervention prevalence of depression between patients who were on oral iron supplementation (n = 37) and those who were not (n = 45).

A sub-group analysis further examined the effect of the intervention on the severity of depression. PHQ-9 scores are categorised into five groups to reflect severity: none (0-4 points), mild (5-9 points), moderate (10-14 points) moderately-severe (15-19 points) and severe (20-27 points) [15]. There was a significant downgrade of depression category from pre- to post-intervention $p < 0.001$ (Figure 2). There were no participants in the severe category at either the pre- or post-intervention stage.

To analyse the relationship between anaemia

Table 1: Baseline demographics of study participants, planned operation and medical history. Values are mean (SD) or number (proportion).

Baseline demographics	
Age (years)	39.6 (6.6)
Weight (kg)	76.1 (15.9)
Planned Operation	
Fibroid resection (open, transcervical or laparoscopic)	58 (72%)
Hysterectomy (open or vaginal or laparoscopic)	19 (23%)
Other	4 (5%)
Medical history	
ASA score	
1	2 (2%)
2	79 (96%)
3	1 (1%)
Current diagnosis of depression	1 (1%)
Current diagnosis of anxiety	5 (6%)
Current diagnosis of depression and anxiety	8 (10%)
On antidepressant medication	4 (5%)
Anaemia diagnosis at time of referral	70 (85%)
Current oral iron therapy	37 (46%)

Table 2: Pre- and post-intervention haemoglobin, ferritin and iron study laboratory tests, Paired Sample T test.

		Mean	n	Standard Deviation	Mean difference	p value
Haemoglobin ($g.l^{-1}$)	Pre	97.0	82	13.2	23.0	$p < 0.001$
	Post	120.0	82	11.2		
Ferritin ($\mu g.l^{-1}$)	Pre	14.2	82	19.0	257.7	$p < 0.001$
	Post	272.0	82	195.3		
Iron saturations (%)	Pre	9.5	82	10.5	15.6	$p < 0.001$
	Post	25.1	82	8.2		

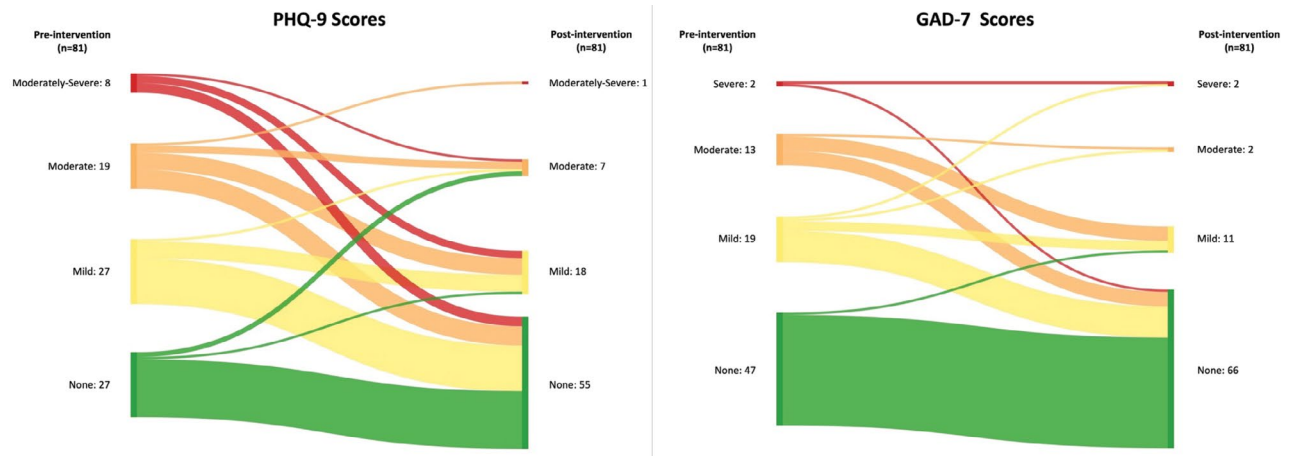

Figure 2: Sankey diagrams showing subgroup analysis based on severity of depression (PHQ-9 scores) pre- and post-intervention, $p < 0.001$ (left) and anxiety (GAD-7 scores) pre- and post-intervention, $p < 0.001$ (right).

severity and depression prevalence, further subgroup analysis was performed, classifying patients according to pre-intervention Hb levels (mild-moderate anaemia: Hb 100-119 $g.l^{-1}$; severe anaemia: Hb < 100 $g.l^{-1}$). Chi-Square testing demonstrated a significant reduction in the prevalence of post-intervention depression in the severe anaemia group (2%), compared with the mild-moderate anaemia group (18%), $p = 0.019$ (Table 5).

Our secondary outcomes investigated the effect of

Table 3: Pre-and Post-intervention Patient Health Questionnaire-9 (PHQ-9) and Generalised Anxiety-Disorder-7 (GAD-7) scores (continuous data), Paired Sample T test.

	Mean	n	Standard Deviation	Standard error of the mean	Mean difference	t	p value
PHQ-9 Score - Pre	7.68	81	4.987	0.554			
PHQ-9 Score - Post	3.72	81	3.796	0.422	3.96	7.024	p < 0.001
GAD-7 Score - Pre	4.93	81	4.541	0.505			
GAD-7 Score - Post	2.56	81	3.619	0.402	2.370	5.425	p < 0.001

Table 4: Pre- and post-intervention Patient Health Questionnaire-9 (PHQ-9) and Generalised Anxiety-Disorder-7 (GAD-7) scores where PHQ-9 greater than or equal to 10 indicates depression and GAD-7 greater than or equal to 10 indicates anxiety, Wilcoxon test.

		Pre-intervention (n = 81)	Post-intervention (n = 81)	p value
		n (%)	n (%)	
PHQ-9 ≥ 10	Yes	27 (33%)	8 (10%)	p < 0.001
	No	55 (67%)	73 (90%)	(Z = -7.508)
GAD-7 ≥ 10	Yes	15 (18%)	4 (5%)	p < 0.001
	No	67 (82%)	77 (95%)	(Z = -8.134)

Table 5: Subgroup analysis of pre-intervention anaemia severity and pre- and post-intervention Patient Health Questionnaire-9 (PHQ-9) ≥ 10 prevalence.

	Pre-intervention Hb		
	Mild-moderate anaemia Hb 100-119 g.l^{-1}	Severe anaemia Hb < 100 g.l^{-1}	p-value
n	40	42	
Pre-intervention PHQ-9 ≥ 10	12 (30.0%)	15 (36%)	0.582 $\chi^2 = 0.303$
Post-intervention PHQ-9 ≥ 10	7 (18.0%)	1 (2%)	0.019 $\chi^2 = 5.506$

χ^2: Chi-squared test; Hb = Haemoglobin

our intervention on anxiety. Pre- and post-intervention GAD-7 scores were 4.93 and 2.56 respectively, mean difference 2.37, p < 0.001 (Table 3). Anxiety was defined as a GAD-7 score of more than or equal to ten. The pre- and post-intervention prevalence of anxiety was 18% and 5% respectively, p < 0.001 (Table 4). A sub-group analysis further examined the effect of the intervention on the severity of anxiety. GAD-7 scores are categorised into 4 groups to reflect severity: None (0-4 points), mild (5-9 points), moderate (10-14 points) and severe (15-21 points) [16]. There was a significant downgrade of anxiety category from pre- to post-intervention, p < 0.001 (Figure 2).

The relationship between the degree of iron depletion and mood disorder prevalence was analysed. The total iron-dose required was used as a surrogate marker of severity of iron-deficiency, and it was compared with the difference in PHQ-9 scores pre- and post-intervention. As the iron-dosing requirement increased from 1000 mg through to 2000 mg, there was a statistically significant greater paired mean difference of PHQ-9 scores. Likewise, comparison for GAD-7 scores demonstrated a statistically significant greater paired mean difference of GAD-7 scores with increasing iron dosing (Table 6).

Discussion

Main findings

Our study demonstrated a high prevalence of depression in women awaiting planned gynecological surgery. This was significantly reduced following our intervention of intravenous iron replacement.

We have demonstrated that intravenous iron administration is significantly associated with both repletion of iron stores and Hb increment, as proven with laboratory testing. Furthermore, the intervention was associated with a significant improvement in depression and anxiety scores, the primary and secondary outcome respectively. A subgroup analysis of both the PHQ-9 and GAD-7 scores demonstrated a significant reduction of disease severity using a standard classification.

We undertook two subgroup analyses to further understand the separate role of anaemia and iron-

Table 6: Subgroup analysis of administered dose of intravenous iron (a marker of severity of iron-deficiency) and mean change (paired samples t-test differences) in pre- and post-intervention Patient Health Questionnaire-9 (PHQ-9) and Generalised Anxiety-Disorder-7 (GAD-7) scores.

Iron dose (mg)	n	Mean difference	SD	t	p
PHQ-9 (n = 81)					
1000	26	2.54	5.70	2.271	0.032
1500	30	4.03	4.67	4.729	< 0.001
2000	25	5.36	4.64	5.781	< 0.001
GAD-7 (n = 81)					
1000	26	1.81	2.99	3.08	0.005
1500	30	2.43	5.20	2.56	0.016
2000	25	2.88	2.99	4.82	< 0.001

SD: Standard Deviation

requirement on mood scores. Firstly, and interestingly, there was no difference in baseline depression prevalence when comparing mild-moderate versus severe baseline anaemia. However, those with severe anaemia demonstrated a significantly greater improvement in depression scores following iron correction, versus those with mild-moderate anaemia. Secondly, when comparing iron-requirement (i.e., the calculated dose of iron needed to correct the iron-deficiency), women requiring higher doses of intravenous iron showed a greater reduction in both depression and anxiety scores.

Strengths and limitations

One of the major strengths of our study is the strict inclusion criteria ensuring only adult females with laboratory confirmed absolute IDA awaiting elective gynecology surgery were enrolled. Furthermore, the validity of the timing of our mood-scoring is appropriate as we have undertaken initial-scoring with confirmed IDA and post-scoring with confirmed effective resolution of IDA. Unlike previous studies [5] evaluating the benefits of a standard fixed dose of intravenous iron, we have ensured each of our enrolled patients have had intravenous iron replenishment with a weight and Hb adjusted dose of iron, and with adequate time for Hb-increment. Finally, we have undertaken adequate investigation and powering of important mental health conditions ahead of gynecology surgery as a primary outcome, and have investigated the subsequent impact of iron replenishment on these outcomes. Traditionally outcomes studied in respect to pre-operative iron therapy are related to post-operative red-cell transfusion or patient morbidity, and in this study we focus on pre-operative mental health.

Our study has several recognized limitations. Firstly, it is not a randomized controlled trial or a case-control study, both of which would have been difficult given our institution's strict protocol and national guidance on optimizing IDA ahead of surgery. As a result, speculating on causation is not possible. Secondly, the pre- and post-intervention mood scoring was undertaken differently: A written questionnaire by the participant only and a telephone questionnaire with a member of the research team respectively. The post-intervention questionnaire was undertaken by telephone to prevent unnecessary travel during the COVID-19 pandemic and to reduce the burden of the study on the participant. We actively chose not to use a postal questionnaire as we felt there may be logistical barriers to completing this within the adequate 48-hour window for the post-intervention laboratory tests as well as reduced compliance. While this is a different method of collecting the data, we do not feel it significantly impacts the results of this study as the telephone questionnaires were conducted in a protocolised manner to best replicate the information provided on the physical form and importantly, we did not inform the participant of their post-intervention blood tests before the questionnaire. Thirdly, perhaps our study could have conducted serial mood scoring post-intervention questionnaires (for example on a weekly basis), to provide more information on the temporal change in mood scores. Finally, a few participants cited the COVID-19 pandemic and the effects of national lockdown as having an impact upon their mood and anxiety levels, which is a confounder that we acknowledge may have affected the results of this study.

Interpretation

The literature reports an association between IDA and depression [7-10]. However, this is the first study to examine this association as a primary outcome in a pre-operative cohort, with effective correction of IDA, and monitoring patient-reported mental health outcomes. The baseline prevalence of depression in this study population, 33%, was higher than that seen generally across several sources [13,17-20], which has a wide variation. Census data from the Office of National Statistics found that 22.5% of women felt some symptoms of anxiety or depression [18].

The data shows an association between mood disorder and IDA, and are in keeping with the few existing studies in the literature [7-10]. Lee, et al. comment on the increased incidence of psychiatric disorders in

patients with IDA10, and Chen et al. demonstrate this association in children and adolescents [7]. Population-based cohort studies have demonstrated a mitigated risk of psychiatric disorders in IDA patients when treated with oral supplementation [10].

The greater improvement in depression and anxiety scores seen in women with severe anaemia and in women requiring higher doses of iron replacement could be in part due to more severe iron-deficiency being associated with higher PHQ-9 scoring as per previous studies [9]. Price has studied a similar patient group to our investigation, females aged 18-45-years, and although they did not demonstrate an association of depression with biochemical anaemia, they did demonstrate an association with symptomatic iron-deficiency [17]. The scientific rationale for iron-deficiency affecting mood includes theories such as central nervous system myelination, monoamine and dopamine neurotransmitter metabolism and serotonin levels [10,21-24]. Perinatal iron-deficiency may lead to long-term behavioural changes despite biochemical correction, which raises the possibility that the central nervous system is susceptible to iron deficiency [22].

A recent randomised controlled trial suggested no benefits of intravenous iron replenishment on co-primary outcomes of mortality and donor blood transfusion, and thus inferred that it should not be recommended in major surgery [5]. Our study differed notably, with more subjective, yet important psychological outcomes in the preparation for surgery; full laboratory diagnostic testing pre- and post-intervention allowing specific recruitment of absolute IDA patients; complete intravenous iron replacement dosing; and administration at least 4-6 weeks ahead of surgery for full Hb optimisation.

Improving depression and anxiety pre-operatively has the potential for significant improvements in patient perioperative outcomes. Pre-operative depression and anxiety have been linked to worse post-operative pain scores and increased length of stay [25] and are associated with poorer psychological outcome after gynaecological surgery [26]. A systematic review of prehabilitation programmes encompassing psychological support demonstrated improved outcomes [27]. There may additionally be a wider scope of benefit outside of gynaecological surgery, with pre-operative depression and anxiety associated with poorer outcomes following cardiac surgery [28]; worse surgical and functional outcomes following radical prostatectomy [29]; worse patient reported outcomes after hip and knee arthroplasty [30] and increased readmission rates after knee arthroplasty [31]. In colorectal surgery, depression was associated with poorer in-hospital outcomes such as wound infection and anastomotic leak [32]. In these patients, depression and anxiety prevalence may be as high as 57% and 47% respectively [33], and up to 75% of patients may be anaemic [34], of whom, the vast majority have absolute iron deficiency [35]. In what is already an established intervention in such patients, iron replenishment may have additional unrecognised benefits, reducing depression and anxiety levels and by extension, improving outcomes.

Conclusion

In conclusion, effective pre-operative correction of IDA with intravenous iron infusion reduces the prevalence of depression and anxiety in patients awaiting gynecological surgery. This should be further explored for the possible implications on the pre-operative pathway in terms of improving mood disorders ahead of surgery, and more effective prehabilitation or engagement with surgery, as well as perioperative outcomes and overall satisfaction.

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Disclosure of Interests

CT declares conference travel expenses from Pharmacosmos and honorarium from Vifor Pharma.

Ethics

This study was submitted via the Integrated Research Application System (IRAS) and gained ethical approval on 21st December 2020 following review by the London Bridge Research Ethics Committee (IRAS Project ID 290558, REC Reference 20/PR/0744). It received Health Research Authority approval on the same date.

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Contribution to Authorship

DW, AV and CT contributed to the conceptualisation and design of the study. DW, HKC and CT provided overall guidance. DW, HKC, JH, SN, AV and CT were involved in data analysis and interpretation. DW, HKC, JH, SN, AV and CT drafted the manuscript. All authors read and approved the manuscript.

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