

Impact Of Iron-Folic Acid Prescribing And Counseling In Gestational Anaemia – A Prospective Study

¹Dr.Dharmapuri Sasasvi, ² Allugani Manish Goud, ³CH.HarshaVardhan, ⁴ Ciddenti Omeshwari,⁵ Dr.Chandrasekhara Rao Baru.

¹ Assistant professor, ²Student,³Student, ⁴Student,⁵ principal.
¹Pharmacy Practice,
¹Chilkur Balaji College of Pharmacy Hyderabad, India

Abstract : Gestational anemia continues to be a public health problem, especially in developing nations like India, where iron deficiency accounts for the highest number of cases. Treatment of gestational anemia is through the administration of iron and folic acid supplements. However, the efficiency of treatment is dependent on not just proper prescribing but also counselling and adherence to the prescribed regimen. This study attempts to determine the effect of adequate prescribing of iron and folic acid supplements and effective counselling on the levels of hemoglobin as well as on patient adherence. Proper prescribing entails giving the right doses of iron and folic acid and for the right duration of time according to medical standards. Through proper counselling, patients learn more about taking their drugs, changing their diet, dealing with side effects and sticking to the regimen. Results show that both proper prescribing and effective counselling result in high levels of hemoglobin and reduced instances of pre-term deliveries, low birth weights and maternal fatigue. Adherence was higher in counselled patients than those who did not receive any counseling. In summary, clinical pharmacy services, which entail patient counseling in addition to prescribing, improves the efficacy of treatments of gestational anemia.

IndexTerms - Gestational anemia, Iron deficiency anemia, Iron-folic acid therapy, Patient counseling, Haemoglobin, Drug compliance, Maternal health, Antenatal clinic visits, Nutritional deficiency, Clinical pharmacy intervention, Folic acid, Iron administration

INTRODUCTION

Anaemia is a global public health issue that disproportionately affects pregnant women. [1] According to WHO estimates, anaemia affects 38.2% of pregnant women worldwide and accounts for 20% of maternal mortality in underdeveloped nations. [11, 14] Iron-folic acid (IFA) supplementation is the cornerstone of prevention and therapy, but poor adherence, insufficient counselling, and inappropriate prescription often hinder its effectiveness. [18, 30] This study examines the effects of pharmacist-led counselling and IFA prescriptions on haemoglobin levels in women with pregnant anaemia. [8]

1.2. DEFINITION OF ANAEMIA

According to the World Health Organization, anaemia is defined as a decrease in blood's ability to carry oxygen because of a lower haemoglobin concentration or RBC count, which is insufficient to fulfil physiological demands. [1] Hb < 12.0 g/dL for non-pregnant women and < 11.0 g/dL (first/third trimester) or < 10.5 g/dL (second trimester) for pregnant women. Functionally, anaemia reduces the amount of oxygen that reaches tissues, which causes compensatory reactions such as increased cardiac output, redistribution of blood flow, and improved tissue oxygen extraction [1, 2, 3]

1.3. TYPES OF ANAEMIA — SIGNS, SYMPTOMS & TREATMENT

1.3.1 Microcytic Anaemia (MCV < 80 fL)

Cause: It include sideroblastic anaemia, thalassaemia, and iron deficiency, which is the most prevalent worldwide. [5, 6] During pregnancy, the mother's iron reserves are depleted by the increased foetal iron need and increased blood volume.

Signs and symptoms: Fatigue, pallor, koilonychia, glossitis, pica, and tachycardia are among the signs and symptoms. [12]

Complications: This includes neonatal IDA, LBW, and premature birth [6].

Treatment: IFA during pregnancy; IV iron sucrose for severe cases; oral ferrous sulphate 325 mg BD. [15, 8]

1.3.2 Macrocytic / Megaloblastic Anaemia (MCV > 100 fL)

Cause: Folic acid or Vitamin B12 deficiency impairing DNA synthesis in erythroid precursors. [12, 17]

Signs & Symptoms: Fatigue, glossitis, peripheral neuropathy (B12), megaloblastic madness.

Complications: Neural tube defects (NTD), recurrent pregnancy loss, cognitive impairment. [17]

Treatment: Folic acid 5 mg/day for deficiency; FA 400 mcg/day for prevention; IM B12 1000 mcg for pernicious anaemia. [18]

1.3.3 Normocytic Anaemia (MCV 80–100 fL)

Cause: Acute blood loss, chronic disease, renal failure (\downarrow EPO), mixed deficiencies, physiological haemodilution of pregnancy. [2, 3]

Signs & Symptoms: Pallor, fatigue, exertional dyspnoea.

Treatment: Treat underlying cause; recombinant EPO for renal anaemia; blood transfusion for acute severe cases. [9]

Table 1: Comparative Overview of Anaemia Types

Feature	Microcytic	Macrocytic/Megaloblastic	Normocytic	Hemolytic
MCV (fL)	< 80	> 100	80–100	Variable
Cause	Fe deficiency, Thal.	Folate/B12 deficiency	Chronic disease, Blood loss	Sickle cell, G6PD
Signs	Pallor, koilonychia, pica	Glossitis, neuropathy	Fatigue, pallor	Jaundice, splenomegaly
Key Test	\downarrow Ferritin, \uparrow TIBC	Hyperseg. neutrophils	Normal indices	\uparrow Reticulocytes, LDH
Treatment	Oral/IV Iron + IFA	B12/Folate supplements	Treat cause, EPO	Manage haemolysis

1.4. GESTATIONAL ANAEMIA

1.4.1 Definition & Hb Levels by Trimester

Gestational anaemia (GDA) is defined as Hb below trimester-specific WHO thresholds. Severity: **Mild** (10.0–10.9 g/dL), **Moderate** (7.0–9.9 g/dL), **Severe** (< 7.0 g/dL). [1],[11]

Table 2: WHO Hemoglobin Thresholds by Trimester & Severity

Trimester	Normal (g/dL)	Mild Anaemia	Moderate	Severe
1st (0–12 wks)	≥ 11.0	10.0–10.9	7.0–9.9	< 7.0
2nd (13–27 wks)	≥ 10.5	10.0–10.4	7.0–9.9	< 7.0
3rd (28–40 wks)	≥ 11.0	10.0–10.9	7.0–9.9	< 7.0

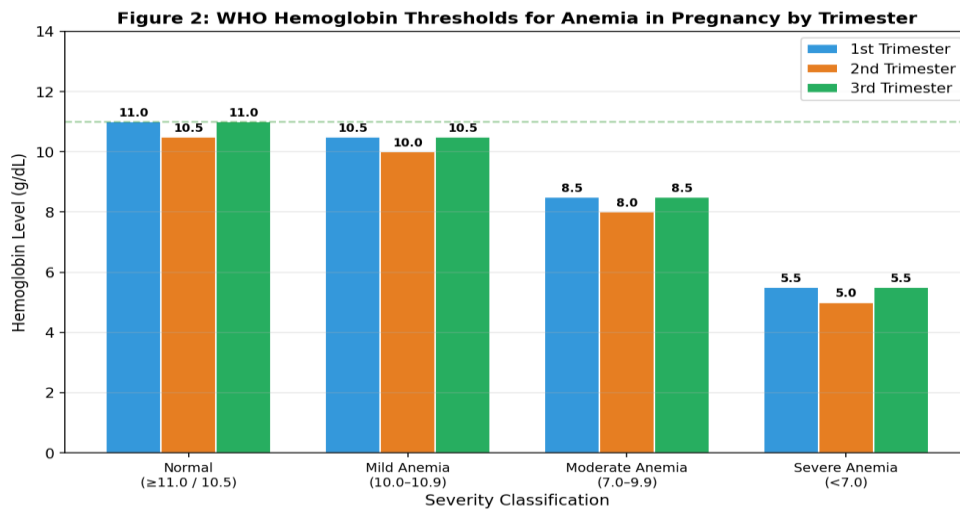


Figure 2: Hemoglobin Thresholds Across Trimesters (WHO Classification)

1.4.2 Epidemiology

Prevalence Anaemia affects 38.2% of pregnant women worldwide (~32 million each year). [11, 14] Sub-Saharan Africa (57%), South Asia (48%), and Southeast Asia (33%) bear the greatest load. [14] According to India's NFHS-5 (2019–21), prevalence among pregnant women was 52%; in rural and adolescent groups, it reached >70%. [10] An estimated 20% of maternal fatalities in underdeveloped countries are related to anaemia. [4]

1.4.3 Nutritional Deficiency Aetiology

- **Iron insufficiency (50%):** Low SF (< 30 ng/mL), high TIBC, and iron requirements increase from 0.8 to 7.5 mg/day across trimesters. [5, 26]
- **Folic acid deficiency (22%):** Associated with megaloblastic anaemia and NTDs; impairs erythropoiesis. [17]
- **Vitamin B12 deficiency:** 8% of vegetarians suffer from vitamin B12 deficiency, which can lead to brain impairment and pernicious anaemia. [12]

Malabsorption Problems

Iron and folate absorption is hampered by *H. pylori* infection, IBD, bariatric surgery, and coeliac disease. [7, 12] Co-administration of calcium supplements and tea polyphenols reduces iron bioavailability by 50–60%. [19]

Genetic Illnesses

RBC survival is altered by sickle cell disease, beta-thalassaemia, and G6PD deficiency, all of which call for treatment beyond basic IFA. [13] These hemoglobinopathies are particularly common in areas where malaria is endemic. [12]

1.4.4 Symptoms and Signs

Mild (Hb 10.0–10.9): exhaustion, palpitations, pallor of the palms and conjunctivae, and dyspnoea with effort. [2, 12]

Moderate (Hb 7.0–9.9): Peripheral neuropathy, glossitis, angular stomatitis, koilonychia, and significant pallor (B12). [3]

Severe (Hb < 7.0): altered awareness, foetal discomfort, cardiac failure, tachycardia (>100 bpm), and dyspnoea at rest. [4, 6]

1.4.5 Pathophysiology:

Pregnancy causes a 45–50% increase in plasma volume and a 20–30% increase in RBC mass, resulting in physiological hemodilution. [3] Iron store depletion → SF → transferrin saturation → TIBC → impaired Hb synthesis → hypochromic microcytic red blood cells [5], [25] Folate deficiency interferes with thymidylate synthesis, which stops DNA replication in erythroid precursors, resulting in nuclear-cytoplasmic asynchrony and ineffective erythropoiesis. [17]

1.4.6 Risk Factors

- **Nutritional:** Inadequate consumption of iron and folate, vegetarianism, and food instability. [7]
- **Obstetric:** numerous gestations, short intervals between pregnancies (<18 months), and multiparity (≥3). [12]

- **Socioeconomic:** Low maternal education, low income, restricted access to ANC, and living in a remote area. [10]
- **Medical:** HIV, malaria, hemoglobinopathies, CKD (including EPO), and coeliac disease. [13]
- **GI/Absorption:** GI blood loss, hyperemesis gravidarum, and consuming tea or calcium together with iron. [7, 30]
- **Pre-existing IDA:** Inadequate iron reserves before to conception are the strongest single predictor. [29]

1.4.7 Complications

Maternal Difficulties

- **PPH:** About 30% $\frac{3}{4}$ risk due to impaired myometrial contractility [4].
- **Infection/Sepsis:** Iron deficiency reduces the bactericidal activity of neutrophils. [24]
- **Heart Failure:** The primary indirect cause of maternal death, chronic severe anaemia leads to high-output failure. [4]
- **Preterm Labour:** 35% $\frac{3}{4}$ chance of preterm contractions due to tissue hypoxia and infection. [22]
- **Maternal Mortality:** In LMICs, it accounts for 20% of maternal fatalities. [11]

Impacts on Infants

- **LBW:** 40% $\frac{3}{4}$ chance of birth weight < 2500 g if Hb < 10 g/dL [6].
- **IUGR:** Foetal oxygen and nutrition supply are restricted by uteroplacental insufficiency. [6, 23]
- **Neonatal IDA:** Foetal iron reserves are depleted by maternal insufficiency, which impairs neurodevelopment. [28, 16]
- **Perinatal Mortality:** Mothers with severe anaemia have a 2-3x increased risk of stillbirth or neonatal mortality. [4]

1.4.8 Diagnostic Tests

A methodical laboratory examination verifies GDA and establishes the cause: [8, 9]

- **CBC:** First line; offers RDW, Hb, Hct, MCV, MCH, and MCHC [8].
- **Peripheral Smear:** target cells (thalassaemia), hypochromic microcytes (IDA), and macro-ovalocytes (folate/B12). [12]
- **Serum ferritin:** It is the best indicator of iron stores; SF < 30 ng/mL indicates IDA; it may be erroneously raised in inflammation. [5]
- **TIBC and serum iron:** transferrin saturation < 16%, SI + TIBC = confirmatory for IDA [5].
- **Serum B12 & Folate:** Megaloblastic anaemia is identified by B12 < 200 pg/mL or folate < 3 ng/mL. [12]
- **Reticulocyte Count:** $\frac{3}{4}$ in aplastic conditions; $\frac{3}{4}$ in haemolysis. [9]
- **Hb Electrophoresis:** Identifies haemoglobinopathies in groups at high risk. [13]

1.4.9 Management & Treatment

Prevention – IFA Supplementation:

Starting with the first ANC check, the WHO advises taking 60 mg of elemental iron and 400 mcg of folic acid daily during pregnancy and the first six weeks after giving birth. [18] The daily intake of iron may be raised to 120 mg in high-prevalence situations (>40%). [11]

Options for Therapy

- **Oral iron:** 325 mg of ferrous sulphate BD/TDS; take with vitamin C on an empty stomach; typical GI side effects are controlled by dividing doses. [30]
- **IV Iron:** For oral intolerance, severe anaemia lasting more than 34 weeks, or malabsorption, provide 200 mg of iron sucrose or 1000 mg of ferric carboxymaltose (single dose). [15]
- **Blood transfusions:** Reserved for patients with symptoms of peripartum haemodynamic impairment and haemoglobin levels less than 7 g/dL. [4]
- **Folic Acid/B12:** B12 1000 mcg IM thrice a month for pernicious anaemia; FA 5 mg daily for megaloblastic anaemia. [17, 18]
- **Dietary counselling:** Avoid tea, coffee, and calcium with IFA; eat iron-rich foods (lean meat, lentils, leafy greens) and vitamin C; monitor adherence at each ANC visit. [24, 19]

1.4.10 Monitoring and follow up

After four weeks, recheck your haemoglobin; an increase of at least 1 g/dL indicates a response. [8] For non-responders, reevaluate adherence, absorption, and continuing losses. [15] To properly replace newborn iron reserves, post-treatment SF > 30 ng/mL is the goal. [26]

2. AIMS AND OBJECTIVES:

2.1 AIMS:

To demonstrate the effectiveness of administering iron-folic acid (IFA) supplements and provide counselling for the treatment and progression of anaemia during pregnancy.

2.2 OBJECTIVES:

1. To determine the degree of haemoglobin alteration in expectant mothers receiving IFA medicine together with counselling.
2. To investigate how counselling supports women's loyalty and stability when using IFA pills while pregnant.
3. To examine clinical data, comprehend the prescription of IFA, and spot recurring trends and deficiencies in medical practice.
 4. To determine the obstacles and variables that encourage pregnant women to consistently take their IFA pills.

3. METHODOLOGY

3.1 STUDY DESIGN:

This is a prospective interventional study design

3.2 STUDY SITE:

The study was conducted in the Outpatient Department (OPD) and Inpatient Department (IPD) of Gynaecology and Obstetrics, Mamatha Academy of Medical Sciences Hospital. Mamatha Hospital is a 1000-bedded multispecialty tertiary care teaching Hospital. The Hospital offers outpatient and inpatient medical services in General medicine, General surgery, orthopaedics, Paediatrics, Pulmonology and Dermatology, Gynaecology and OBG, Neurology, Urology, cardiology and Dental services, and ENT, Ophthalmology. The hospital offers Outpatient Department services on weekdays from 9:00 AM to 4:00 PM. Gynaecology and Obstetrics Outpatient Department Services through three different units on a rotational basis. On average, 50 to 100 Patients visit the GYN & OBG OPD per day.

3.3 STUDY PERIOD:

A study was carried out between September 2025 to February 2026 over a period of 6 months.

3.4 STUDY CRITERIA:

3.4.1 Inclusion criteria:

- Pregnant woman diagnosed with gestational anaemia (Hb<11g/dl)
- Pregnant woman with gestational age between 1 to 9 months
- Patients prescribed iron folic acid supplementation
- Patients willing to provide written informed consent

3.4.2 Exclusion criteria:

- Pregnant women with chronic diseases such as renal or liver disorders.
- Patients with bleeding disorders, Other causes of anaemia, such as thalassaemia or vitamin B12 deficiency

Patient's not willing to participate, incomplete clinical records or inability to follow up

3.5 SOURCE OF DATA:

Data were collected from

- Patient interviews
- Antenatal records
- Case sheets
- Laboratory reports
- Prescription records
- Structured KAP and MARS questionnaire

3.6 VARIOUS STUDY TOOLS USED IN THE STUDY

3.6.1 Knowledge Attitude Practice (KAP) questionnaire:

A Structured KAP questionnaire was used to assess patient awareness regarding gestational anemia, and iron. Folic acid supplementation.

The questionnaire consisted of three domains:

Domain	Questions	Score Type
Knowledge	18	Correct/Incorrect
Attitude	10	Likert scale
Practice	10	Likert scale

3.7 SAMPLE SIZE CALCULATION

Unlimited population:

$$n = \frac{Z^2 * p(1-p)}{d^2}$$

Where:

- n = required sample size
- Z = Z-value for confidence level
- p = expected proportion
- d = margin of error (precision)

3.8 METHOD OF DATA COLLECTION:

Data were collected using:

- Patient interviews
- Antenatal records
- Laboratory investigations
- Structured questionnaires

All data entered into Google forms, Google sheets and SPSS software for statistical analysis.

3.9 STUDY PROCEDURE:

Pregnant woman diagnosed with gestational anaemia (Hb<11g/dL) where enrolled after obtaining informed consent

Baseline data collected included:

- Demographics
- Obstetric history
- Haemoglobin levels
- Prescription details of IFA supplementation
- KAP questionnaire

3.10 FOLLOW-UP SCHEDULE

Visit	Time	Assessments
Baseline	Enrollment	Hb, KAP
First Follow-up	4 weeks	KAP
Second Follow-up	8 weeks	KAP
Final Follow-up	12 weeks	HB, KAP

3.11 PHARMACIST INTERVENTION

Clinical pharmacists provided structured patient education, and counselling covering:

- Importance of iron folic acid supplementation
- Correct dosage and duration
- Dietary sources of iron
- Importance of vitamin C for iron absorption
- Avoiding tea or coffee near IFA intake
- Managing common side effects

Patients were provided with:

- Educational leaflets
- Dietary recommendations
- Medication adherence counselling

Counselling was reinforced at each follow-up visit.

3.12 DATA ANALYSIS:

The following relationships were evaluated:

- Haemoglobin levels and medication adherence
- Effect of pharmacist counselling on KAP course
- Association between adherence and anaemia improvement

3.13 STATISTICAL ANALYSIS OF DATA:

Statistical analysis was performed using SPSS software version 31 for descriptive statistics at a statistical significance of $p < 0.05$

4. RESULTS:

A total of 200 pregnant women diagnosed with gestational anaemia were enrolled in the study from the Department of OBG at Mamatha Hospital. Out of these, 170 pregnant women completed all the follow-ups. 30(7.5%) patients were considered to be dropouts.

4.1 DEMOGRAPHIC DETAILS OF ENROLLED PATIENTS

PARAMETER	FREQUENCY N (%)
Age Group	
18-20	38.8 (19.40%)
21-25	78.8 (39.40%)
26-30	53 (26.50%)
31-35	22.2 (11.10%)
>35	7 (3.50%)
Education	
Illiterate	31.80 (15.9%)
Primary	50.80 (25.4%)
Secondary	74.60 (37.3%)
Higher secondary	28.20 (14.1%)
Graduate	14.6 (7.3%)

The majority of the patients were 21 to 25 Years old (39.4%), had secondary school education (37.3%) and were homemakers (65.9%).

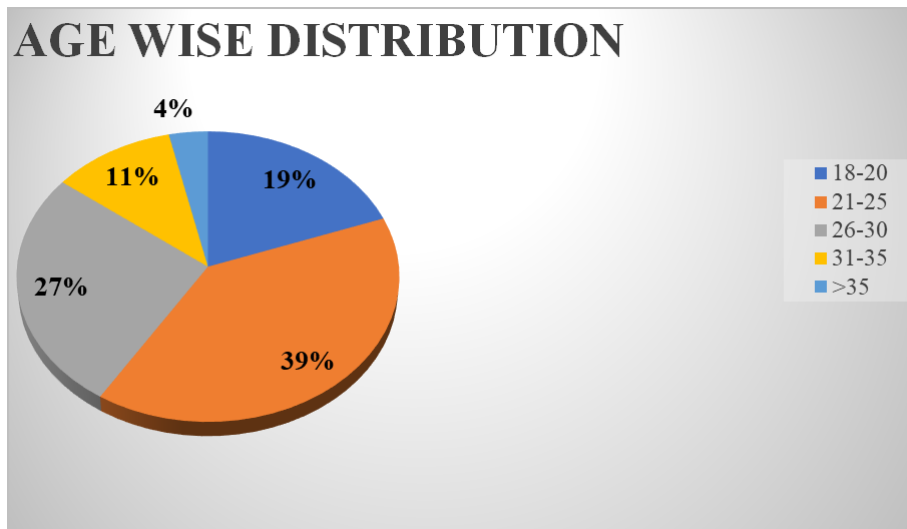


Fig: Age-wise distribution of patients

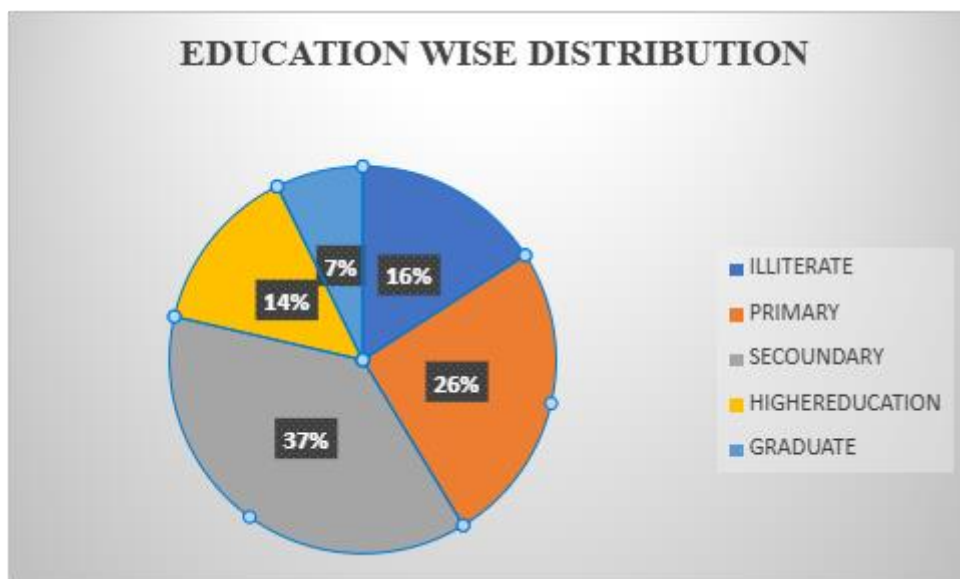


Fig: Education-wise distribution of patients

4.2 TRIMESTER DISTRIBUTION

TRIMESTER	FREQUENCY N(%)
First	36 (22.2%)
Second	107.60 (46.2%)
Third	56.40 (31.6%)

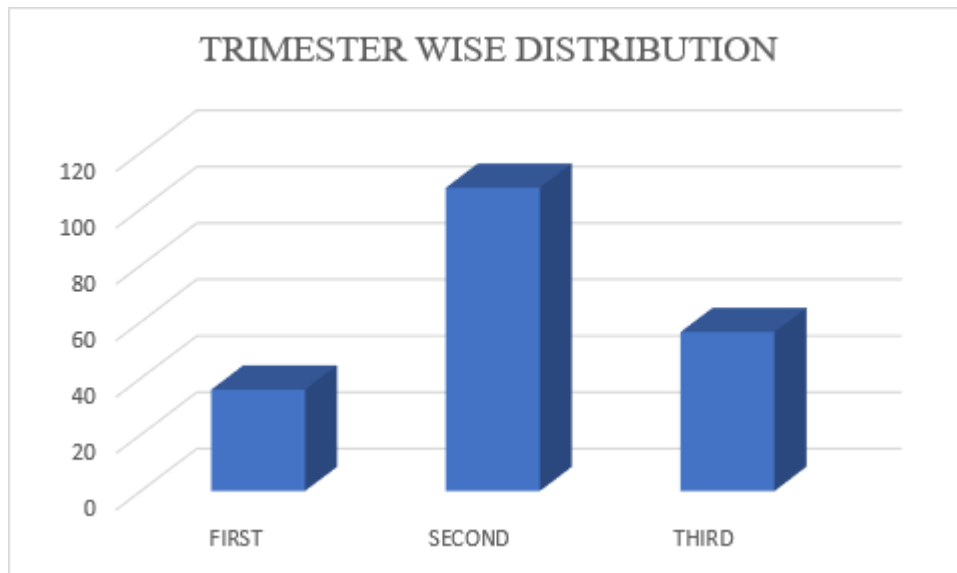


Fig: The majority of the patients enrolled belonged to 2nd trimester, 46.2%.

5.DISCUSSION:

One of the most common conditions affecting pregnant women globally, especially in underdeveloped nations, is gestational anaemia. Serious problems for both the mother and the foetus, such as preterm delivery, low birthweight, and increased maternal morbidity, can result from iron deficiency during pregnancy. The current study was carried out to assess the effects of iron, folic acid supplements, and pharmacist-led advice on haemoglobin levels, medication, adherence, and awareness among expectant mothers with gestational anaemia.

From baseline to the end follow-up, 170 pregnant women with a diagnosis of gestational anaemia were enrolled and monitored for 12 weeks. The improvement in haemoglobin levels, medication adherence as measured by knowledge, attitude, and practice (KAP) on iron supplementation and pregnant anaemia were the main objectives of the study.

According to the research population's demographics, most of the participants were between the ages of 21 and 25, which is in line with India's typical reproductive age range. The majority of participants had only completed high school and were homemakers. These results imply that knowledge of dietary inadequacies and adherence to iron supplementation during pregnancy may be influenced by socioeconomic and educational characteristics.

6.CONCLUSION

The current prospective study assessed the effects of pharmacist-led advice and iron-folic acid supplementation on pregnant anaemia among pregnant women. The study's results showed that among pregnant women who visited the prenatal clinic, gestational anaemia was quite common. Early assessment and treatments are necessary since most of the patients had moderate anaemia at baseline. The study showed that pregnant women's haemoglobin levels were considerably raised by routine iron-folic acid supplementation in conjunction with organised chemist counselling. During the follow-up period, a gradual rise in haemoglobin levels was noted, demonstrating the intervention's efficacy. The study also revealed that after counselling sessions, participants' knowledge, attitudes, and practices about iron supplementation and pregnant anaemia significantly improved. Better health-seeking behaviour and therapy adherence were linked to increased awareness.

7.REERENCES

- [1] World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia. WHO/NMH/NHD/MNM/11.1. Geneva: WHO; 2011.
- [2] Milman N. Postpartum anemia I: definition, prevalence, causes, and consequences. *Ann Hematol.* 2011;90(11):1247–1253.
- [3] Sifakis S, Pharmakides G. Anemia in pregnancy. *Ann N Y Acad Sci.* 2000; 900:125–136.
- [4] Daru J, et al. Risk of maternal mortality in women with severe anaemia. *Lancet Glob Health.* 2018;6(5):e548–e554.
- [5] Breyman C. Iron deficiency anemia in pregnancy. *Semin Hematol.* 2015;52(4):339–347.

- [6] **Kozuki N**, Lee AC, Katz J. Maternal anemia and risk of small-for-gestational-age outcomes. *J Nutr.* 2012;142(2):358–362.
- [7] **Okwu GN**, Ukoha AI. Predisposing factors of iron deficiency anaemia in pregnant women. *Pak J Nutr.* 2008;7(1):151–156.
- [8] Pavord S, et al. UK guidelines on management of iron deficiency in pregnancy. *Br J Haematol.* 2012;156(5):588–600.
- [9] **Schrier SL**, Auerbach M. Treatment of iron deficiency anemia in adults. *UpToDate.* 2022.
- [10] **Kalaivani K**. Prevalence and consequences of anaemia in pregnancy. *Indian J Med Res.* 2009;130(5):627–633.
- [11] **World Health Organization**. Global Nutrition Targets 2025: Anaemia Policy Brief. WHO/NMH/NHD/14.4. Geneva: WHO; 2014.
- [12] **Goonewardene M**, Shehata M, Hamad A. Anaemia in pregnancy. *Best Pract Res Clin Obstet Gynaecol.* 2012;26(1):3–24.
- [13] **Van den Broek NR**, Letsky EA. Etiology of anemia in pregnancy in south Malawi. *Am J Clin Nutr.* 2000;72(1S):247S–256S.
- [14] **Stevens GA**, et al. Global trends in haemoglobin concentration and prevalence of anaemia 1995–2011. *Lancet Glob Health.* 2013;1(1):e16–25.
- [15] **Revez L**, et al. Treatments for iron-deficiency anaemia in pregnancy. *Cochrane Database Syst Rev.* 2011;(10):CD003094.
- [16] **Gambling L**, McArdle HJ. Iron, copper and fetal development. *Proc Nutr Soc.* 2004;63(4):553–562.
- [17] **Allen LH**. Anemia and iron deficiency: effects on pregnancy outcome. *Am J Clin Nutr.* 2000;71(5S):1280S–1284S.
- [18] **Peña-Rosas JP**, et al. Daily oral iron supplementation during pregnancy. *Cochrane Database Syst Rev.* 2015;(7):CD004736.
- [19] **Yip R**. Iron deficiency: international programmatic approaches. *J Nutr.* 1994;124(8S):1479S–1490S.
- [20] **De Maeyer E**, Adiels-Tegman M. The prevalence of anaemia in the world. *World Health Stat Q.* 1985;38(3):302–316.
- [21] **Steer P**, et al. Maternal haemoglobin concentration and birth weight by ethnic group. *BMJ.* 1995;310(6978):489–491.
- [22] **Rasmussen KM**. Iron deficiency and perinatal mortality. *J Nutr.* 2001;131(2S):590S–601S.
- [23] **Cogswell ME**, et al. Iron supplementation, anemia, and birth weight: RCT. *Am J Clin Nutr.* 2003;78(4):773–781.
- [24] **Black RE**, et al. Maternal and child undernutrition in LMICs. *Lancet.* 2013;382(9890):427–451.
- [25] **Pasricha SR**, et al. Control of iron deficiency anemia in LMICs. *Blood.* 2013;121(14):2607–2617.
- [26] **Milman N**. Iron in pregnancy: securing appropriate status. *Ann Nutr Metab.* 2011;59(1):50–54.
- [27] **Friedman AJ**, et al. Iron deficiency anemia in women across the life span. *J Womens Health.* 2012;21(12):1282–1289.
- [28] **Georgieff MK**. Iron deficiency in pregnancy. *Am J Obstet Gynecol.* 2020;223(4):516–524.