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Maternal Anemia in Pregnancy: An Overview

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ABSTRACT

Anemia is the commonest medical disorder in pregnancy and severe anemia is associated with poor maternal and perinatal outcome. It is one of the most important health problems among women from 18 to 45 years of age in the world. Anemia in pregnancy is considered as one of the major risk factors for contributing 20-40% of maternal deaths directly or indirectly through cardiac failure, preeclampsia, antepartum haemorrhage, postpartum haemorrhage and puerperal sepsis. As well as to low birth weight which in turn might contribute to increased percentage for infant mortality in developing countries. The prevalence of anemia in pregnancy varies considerably because of differences in socioeconomic conditions, lifestyles and health seeking behaviors across different cultures. Women of low socio-economic groups and teenagers are more susceptible towards anemia during pregnancy. More commonly, anemia in pregnancy is due to lack of iron and less often, it is caused by folic acid deficiency. Iron and folate supplementation is indicated during pregnancy to prevent the complications. In normal pregnancy, the hemoglobin concentration becomes diluted according to the increase in the volume of circulating blood. Anemia is diagnosed by estimating the hemoglobin concentration and examining a peripheral blood smear for the characteristic red blood cell changes.

INTRODUCTION

Maternal Anemia is an extremely serious public health problem in developing countries during pregnancy. Anemia has severe nutritional and health consequences, including high maternal mortality, inadequate growth and impaired mental development in children. Anemia during pregnancy increases the risk of fetal growth retardation and low birth weight, premature delivery, increased perinatal mortality, and reduced resistance to infection of both mother and baby. Anemia also results in decreased work capacity, including reduced care giving and general productivity. The etiology of anemia is complex. Pregnancy is natural phenomenon and a woman's life is not complete until she becomes a mother. Women as a supreme creature of God go through a variety of physiological changes during pregnancy. Changes in the blood circulatory system are particularly notable, permitting normal fetal growth. About 20% of pregnant women suffer anemia, and most of the cases are iron deficiency, folic acid deficiency, or both [1].

Anemia is the commonest medical disorder in pregnancy and has a varied prevalence, etiology and degree of severity in different populations being more common in non-industrial countries [2]. The World Health Organization (WHO) estimates that two billion people over 30% of the world's populations are anemic, although prevalence rates are variable because of differences in socioeconomic conditions, lifestyles, food habits, and rates of communicable and non-communicable diseases [3]. The lowest normal hemoglobin in the healthy non-pregnant woman is defined as 12g/dl. The World Health Organization (WHO) recommends that hemoglobin ideally should be maintained at or above 11.0 g/dl, and should not be allowed to fall below 10.5 g/dl in the second trimester [4]. As per WHO guidelines, Anemia is classified as

(1) Mild anemia (Hb 10 to 10.9 g/dl);
(2) Moderate anemia (Hb 7 to 9.9 g/dl);
(3) Severe anemia (Hb less than 7 g/dl);
(4) Very severe (Hb less than 4 g/dl).

Iron absorption during pregnancy is determined by the amount of iron in diet, its bioavailability and the changes in iron absorption that occur during pregnancy. An acid environment in the duodenum helps in the absorption of iron. The frequent ingestion of antacids and chronic use of

H2 blockers and proton pump inhibitors diminishes the iron absorption. Vitamin C, in addition to the iron, may increase acid environment of the stomach and increase absorption. Iron requirements are greater in pregnancy than in non-pregnant state. Although iron requirements are reduced in the first trimester because of absence of menstruation these raise steadily thereafter as high as ≥10 mg/day [5]. The amounts that can be absorbed from even an optimal diet, however are less than the iron requirement in later pregnancy and a women must enter pregnancy with iron stores of >300 mg if she is to meet her requirement fully [6]. Iron requirements are increased in pregnancy, especially in the third trimester when they may be several times higher than at other stages of the life cycle, the net iron requirements for pregnancy are 840 mg approximately [7]. Anemia is responsible for 20-40% of maternal deaths directly or indirectly through cardiac failure, preeclampsia, antepartum haemorrhage, postpartum haemorrhage and puerperal sepsis [8].

Pregnancy induced hypertension is five times more common in severe anemia and significant proportion of patients had postpartum haemorrhage with severe maternal Anemia [9]. The risk of preterm delivery was four times greater among women with anaemia [10]. Severe maternal anemia has poor outcome of neonates in the form of low birth weight, prematurity, intrauterine growth retardation, intrauterine death and birth asphyxia [11]. A pregnant woman must have at least 500 mg of stored iron to fulfill the requirements of gestation without the need for iron supplementation. Even though this deposit is present it will be completely exhausted by the end of gestation. The total iron requirement during pregnancy is 700-1400 mg. Overall requirements is 4mg-6mg per day, but this increases to 6-8 mg per day in the last weeks of pregnancy. Anemia is not only responsible for increase in perinatal and maternal mortality but also severely affects economic and social status of the country. There are many studies on anemia in pregnancy in Nepal.

Anemia is a lack of functioning red blood cells (RBCs) that leads to a lack of oxygen-carrying ability, causing unusual complications during life time. These RBCs are produced in the bone marrow. They have a life expectancy of about 120 days. Among other things, the body needs iron, vitamin B12 & folic acid for erythropoiesis. If there is a lack of one or more of these ingredients or there is an increased loss of RBCs, anemia develops. Any patient with Hb of less than 11 gm/dl to 11.5 gm/dl at the start of pregnancy will be treated as anemic. The reason is that as the pregnancy progresses, the blood is diluted and the woman will eventually become anemic. The dilution of blood in pregnancy is a natural process and starts at approximately at the eighth week of pregnancy and progresses until the 32nd to 34th week of pregnancy [12]. Anemia is a condition in which the number of red blood cells and their oxygen carrying capacity is insufficient to meet the body's physiological needs. RBCs plays a role to deliver oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs which is facilitated by hemoglobin, a tetramer protein composed of haem and globin. The reduction in the number of RBCs transporting oxygen and carbon dioxide results in impairment of gas exchange and this is due to anemia which may be either due to defective red cell production, increased red cell destruction or blood loss. Iron is necessary for synthesis of hemoglobin. Iron deficiency is thought to be the most common cause of anemia globally, but other nutritional deficiencies (including folate, vitamin B12 and vitamin A), acute and chronic inflammation, parasitic infections, and inherited or acquired disorders that affect Hb synthesis, red blood cell production or red blood cell survival also result in anemias. Iron deficiency anemia results in impaired cognitive and motor development in children and decreased work capacity in adults. The effects are most severe in infancy and early childhood. In pregnancy, iron deficiency anemia can lead to perinatal loss, prematurity and low birth weight babies. Iron deficiency anemia also adversely affects the body's immune response. The most common types of anemia are- iron deficiency anemia, Thalassaemia, Aplastic anemia, Haemolytic anemia, Sickle cell anemia, Pernicious anemia, Fanconi anemia. Iron deficiency is the most prevalent cause of anemia which is usually due to chronic blood loss caused by excessive menstruation increased demand for iron, such as fetal growth in pregnancy [13]. Anemia can occur at any age and affect either gender, although it is more prevalent in pregnant women and young children [14]. The major risk groups for iron deficiency include women of childbearing age, pregnant women, and lactating postpartum women [15]. Maternal consequences of anaemia are also well known and include cardiovascular symptoms, reduced physical and mental performance, reduced immune function, tiredness, reduced peripartal blood reserves and finally increased risk for blood transfusion in the postpartum period. For clinical management, proper diagnosis and therapy are mandatory to reduce maternal and fetal risks and to enable optimal obstetrical outcome of both.

Maternal Changes during Pregnancy

During pregnancy, there is an increase in both red cell mass and plasma volume to accommodate the needs of the growing uterus and fetus. The circulating plasma volume increases linearly to reach a plateau in the 8^{th} or 9^{th} month of pregnancy. The increment is about 1000 ml, which corresponds to 45% of the circulating plasma volume in non-pregnancy. The plasma volume decreases rapidly after delivery and is then restored to the non-pregnancy level at about 3 puerperal weeks. However, plasma volume increases more than the red cell mass leading to a fall in the concentration of hemoglobin in the blood, despite the increase in the total number of red cells. This drop in hemoglobin concentration decreases the blood viscosity and it is thought this enhances the placental perfusion providing a better maternal-fetal gas and nutrient exchange [16].

Physiological hemo dilution of pregnancy and at what level of hemoglobin, women and babies would get benefit from iron treatment. Some studies suggest that the physiological decrease in hemoglobin is associated with improved outcomes for the baby. An adult woman has about 2,000 mg iron in the body, 60–70% of which is present in erythrocytes, with the rest stored in the liver, spleen, and bone marrow. When a woman becomes pregnant, the demand for iron increases. Specifically, about 1,000 mg more is required, comprising 300 mg for the fetus and placenta, 500 mg for increased maternal hemoglobin, and 200 mg that compensates for excretion. Therefore, an additional 50% of the amount of iron present in the non-pregnant state should be ingested during pregnancy [17].

Iron Deficiency Anemia during Pregnancy

Iron deficiency anemia (IDA) is the most common cause of nutritional anemia. Poor absorption of iron is aggravated by diet rich in phytates and phenolic compounds which prevent absorption of iron thereby resulting in anemic condition. Iron deficiency anemia is characterized by a defect in hemoglobin synthesis, resulting in red blood cells that are abnormally small (microcytic) and contain a decreased amount of hemoglobin (hypochromic) [18]. The capacity of the blood to deliver oxygen to body cells and tissues is thus reduced. Iron is essential to all cells. Functions of iron include involvement in energy metabolism, gene regulation, cell growth and differentiation, oxygen binding and transport, muscle oxygen use and storage, enzyme reactions, neurotransmitter synthesis, and protein synthesis [19]. Approximately 1190 mg of iron is required to sustain pregnancy from conception through delivery [20]. The iron requirement during pregnancy is increased gradually through gestation from 0.8 mg/day in the first trimester to 7.5 mg/day in the third trimester. The average requirement of iron in the entire gestation period is approximately. 4.4 mg/day [21, 22]. The required iron is used to expand the woman's erythrocyte mass, fulfill the fetus's iron requirements, compensate for iron losses (i.e. blood losses) at delivery. The newborns body iron content depends to a large extent on their birth weight. At a low birth weight of approx 2,500 g, the iron content of the newborn is approx 200 mg and at a "normal" birth weight of approx 3,500 g, the iron content is approx 270 mg [23]. Maternal iron deficiency in pregnancy increases the neonatal mortality and morbidity [24]. If the hemoglobin level is less than 8 grams/dl, then the risk of death during delivery increases 2-3 folds. Further, if the hemoglobin drops below 5 gm/dl, then the risk of death increases 8-10 folds [25]. The low maternal hemoglobin concentration is more likely to result in preterm delivery and thus low fetal birth weight [26]. .

Classification of anemia in pregnancy

Anemia is grossly classified into two types:
(A) Pathological anemia in pregnancy.
(B) Physiological anemia in pregnancy.

(A) Pathological Anemia: It is further sub-classified into:

1. Deficiency Anemia: e. g. -Iron deficiency -Folic acid deficiency -B12 deficiency -Protein deficiency.

2. Hemorrhagic:

Acute hemorrhagic: Following bleeding in early month of pregnancy or APH

Chronic hemorrhagic: as by hookworm infestation, GI (gastrointestinal) bleeding.

Hereditary: Thalassemias – Haemolobinopathies. This is due to:

a. Faulty dietary habit,

b. Faulty absorption mechanism,

c. More iron loss due to sweating and repeated pregnancy at short interval; prolonged period of lactation,

d. Infection: Chronic malaria, tuberculosis, e. Excess demand of iron: pregnancy is an iron deficit state

(B) Physiological Anemia: During pregnancy there is disproportionate increase in plasma volume upto 50%, RBC 33% and Hb 18-20% mass. In addition there is marked demand of extra iron during pregnancy especially in the second half of pregnancy. So, physiological anemia is due to combined effect of hemodilution & negative iron balance.

Criteria of Physiological Anemia include [27]

- Hb% - 10 gm or less,
- R.B.C – 3.5 million/mm3,
- P.C.V – 30%, -
- PBF – Normal morphology with central pallor.

Clinical features of iron deficiency anemia depends more on the degree of anemia.

Symptoms of anemia include lassitude, feeling of exhaustion, weakness, anorexia, indigestion, palpitation; swelling legs Signs of anemia include pallor, glossitis, Stomatitis, edema legs, soft systolic murmur in mitral area. Investigations are done to detect the degree of anemia, the type of anemia the cause of anemia. To ascertain the degree of anemia one must look for Hb%, RBC count, PCV (Packed Cell Volume). Mild anemia means Hb- 8-10 gm%; Moderate- less than 7-8 gm%; Severe–Less than 7 gm%. To determine type of anemia one must examine the PBF (Peripheral Blood Film), hematological indices like MCV, MCH, MCHC, etc.

A typical iron deficiency anemia shows the flowing blood values:

- Hb-less than 10 gm%
- RBC – less 4 million/ mm3
- PCV – less than 30%
- MCHC – Less than 30%
- MCV – less than 75% micro mole m3 (meter cube)

- MCH- less than 25 pg. Serum iron is usually below 30 micro gram/ 100 ml.

Total iron binding capacity increases to 400 micro gram/100ml. Serum ferritin falls below 15 micro gm/L.

To find out the cause of anemia, the physician should carefully follow the basic protocols.

- History taking,
- Physical examination,
- Routine examination of stool to detect helminthes or occult blood,
- Urine is examined for the protein, sugar and pus cells,
- X ray chest in suspected cases of pulmonary tuberculosis; but in case not responding to therapy, bone marrow study should be undertaken.
- Blood for PBF & malarial parasites,
- Kidney function tests like BUN & creatinine, etc

Maternal consequences of anemia

Mild anemia

Work propensity is decreased in women with mild anemia in pregnancy. They may be unable to earn their livelihood if the work involves manual labour. Women with chronic mild anemia may go through pregnancy and labour without any adverse consequences, because they are well compensated.

Moderate anemia

Women with moderate anemia have considerable reduction in work capacity and may find it difficult to cope with household chores and child care. They are more vulnerable to infections and recovery from infections may be prolonged. Premature births are more common in women with moderate anemia. They deliver infants with lower birth weight and prenatal mortality is higher in these babies. They may not be able to bear blood loss prior to or during labour and may succumb to infections more readily. Substantial proportion of maternal deaths due to antepartum and post-partum haemorrhage, pregnancy induced hypertension and sepsis occur in women with moderate anemia. [28].

Severe anemia

Three distinct stages of severe anemia have been recognized - compensated, decompensated, and that associated with circulatory failure. Cardiac decompensation usually occurs when Hb falls below 5.0 g/dl. The cardiac output is raised even at rest, the stroke volume is larger and the heart rate is increased. Palpitation and breathlessness even at rest are symptoms of these changes. These compensatory mechanisms are inadequate to deal with the decrease in Hb. levels. Oxygen lack results in anaerobic metabolism and lactic acid accumulation occurs. Eventually circulatory failure occurs restricting work output. Untreated, it leads to pulmonary edema and death. When Hb is <5 g/dl and packed cell volume (PCV) below 14 [29]. A blood loss of even 200 ml in the third stage produces shock and death in these women. Even today women in the remote rural areas in India reach to the hospital only at this late decompensate stage. Available data from India indicate that maternal morbidity rates are higher in women with Hb below 8.0 g/dl. Maternal mortality rates show a steep increase when maternal Hb levels fall below 5.0 g/dl.

Pregnancy Maternal effects of Anemia

The effect of maternal anemia on the foetus indicates that different types of decomposition occur with varying degrees of anemia. Most of the studies suggest that a fall in maternal hemoglobin below 11.0 g/d1 is associated with a significant rise in perinatal mortality rate18, 19, and 25. There is usually a 2 to 3-fold increase in perinatal mortality rate when maternal hemoglobin levels fall below 8.0 g/d1 and 8-10 fold increase when maternal hemoglobin levels fall below 5.0 g/dl. A significant fall in birth weight due to increase in prematurity rate and intrauterine growth retardation has been reported when maternal hemoglobin levels were below 8.0 g/d1. [30,31,]. Mild, anemia may not have any effect on pregnancy and labour except that the mother will have low iron stores and may become moderately to- severely anemic in subsequent pregnancies. Moderate anemia may cause increased weakness, lack of energy, fatigue and poor work performance. Severe anemia, however, is associated with poor outcome. The woman may have palpitations, tachycardia, breathlessness, increased cardiac output leading on to cardiac stress which can cause de-compensation and cardiac failure which may be fatal [32,33]. Increased incidence of pre-term labour (28.2%), pre-eclampsia (31.2%) and sepsis have been associated with anemia [32]. Irrespective of maternal iron stores, the fetus still obtains iron from maternal transferrin, which is trapped in the placenta and which, in turn, removes, and actively transports iron to the fetus. Gradually, however, such fetuses tend to have decreased iron stores due to depletion of maternal stores. Adverse perinatal outcome in the form of pre-term and small-for-gestational-age babies and increased perinatal mortality rates have been observed in the neonates of anemic mothers. Iron supplementation to the mother during pregnancy improves perinatal outcome. Mean weight, Apgar score and haemoglobin level 3 months after birth were significantly greater in babies of the supplemented group than the placebo group.

Clinical Signs and Symptoms

Pregnancy anemia can be asymptomatic and may be diagnosed following routine screening. The signs and symptoms are often non-specific with tiredness being the most common. Women may also complain of weakness, headaches, palpitations, dizziness, dyspnoea and hair loss. Signs of anemia can occur in the absence of a low Hb.

Diagnosis

Knowledge of different hemoglobin cut off levels during pregnancy to differentiate between hydraemia and true anemia is important in the first step of diagnosis. Lower hemoglobin cut off is 11.0 g/dL in the first and last trimester and 10.5 g/dL in the second trimester. Therefore any level below 10.5 g/dL should be regarded as anemia and consequently checked. The next step includes differential diagnosis of anemia. Iron deficiency the major cause of anemia during pregnancy, but others such as infection, abnormal hemoglobin, renal disease or parasites (malaria, worms) must be ruled out before therapy starts to guarantee optimal therapeutic effects A trial of oral iron therapy can be both diagnostic and therapeutic. If hemaglobinopathy status is unknown, then it is reasonable to start oral iron therapy whilst screening is carried out. A trial of oral iron should demonstrate a rise in Hb within 2 to 3 weeks. If there is a rise then this confirms the diagnosis of iron deficiency. If there is no rise, further tests must be carried out. In patients with a known hemaglobinopathy serum ferritin should be checked first. Ferritin levels below 30µ/l should prompt treatment and levels below 15µ/l are diagnostic of established iron deficiency. Traditional therapeutic options of iron deficiency anaemia in pregnancy were administration of oral iron or in severe cases administration of blood transfusion. While oral iron shows limited effectiveness in cases of severe anaemia due to various factors such as side effects, lack of compliance and often limits intestinal absorption and bioavailability, blood transfusion must be avoided due to considerable transfusion risks such as infections, risk of incorrect transfusion, transfusion reactions and negative impact on the immune system. There are also an increasing number of patients who deny blood transfusion.

Laboratory Parameters

In addition to clinical assessment, laboratory parameters are of major importance for differential diagnosis of anaemia. More than 100 years ago first tests including blood smear, red cell being the actual gold standard of iron status testing. However, in certain conditions such as underlying infections, ferritin is not valuable, since it reacts as an acute phase reactant and shows false normal results, e.g. in the postpartum period. During pregnancy, ferritin shows also weak correlations to other iron parameters and then severity of anaemia, therefore additional tests are helpful.

Hypochromic Red Cells

Hypochromic red cells are released into the blood in cases of severe anaemia, e.g. iron deficiency, or during functional iron deficiency, e.g. erythropoietic stress with insufficient iron supply. Using modern automated red cell analyzer systems it is possible to measure the quantity of hypochromic red cells (HRBC) and the percentage of HRBC of total red cells. These data are helpful to determine the severity of iron deficiency, for differential diagnosis (e.g. thalassaemia vs. iron deficiency) of anaemia, for assessment of functional iron deficiency (e.g. during rhEPO treatment) and finally the monitoring of therapy and its effects, namely decrease of hypochromics due to efficient iron administration.

Soluble Serum Transferrin Receptors

Serum transferrin receptor (sTfR) assay is another important new laboratory test which is increasingly used in obstetrics. STfR are on the surface of every iron incorporating cell and are released into the blood in cases of increased tissue iron needs such as during severe iron deficiency or during forced erythropoiesis. As HRBC, increased sTfR levels indicate functional iron deficiency but also increased erythropoiesis and body iron needs.

Management

NICE guidelines recommend that women are screened for anaemia at booking and again at 28 weeks gestation. All women should be given advice regarding diet in pregnancy with details of foods rich in iron along with factors that may promote or inhibit the absorption of iron. This should be backed up with written information. Dietary changes alone are not sufficient to correct an existing iron deficiency in pregnancy and iron supplements are necessary [33,34].

Prophylaxis

The WHO recommends a daily folate intake of 800 µg in the antenatal period and 600 µg during lactation. However, 300-500 µg present in most iron preparations is enough for prophylaxis [35,36]. Pregnant women should eat more green vegetables (e.g. spinach and broccoli) offal (e.g. liver and kidneys). Folate is destroyed by cooking. Even food fortification with folic acid is recommended and is already in use in Western countries.

Prescribing Iron Supplements and Follow-up :

- The type, frequency, and duration of the treatment or medication.
- Side-effects of the medication which can exacerbate the symptoms of pregnancy including heartburn, nausea, vomiting and constipation.
- Management of side-effects.
- How and when to take the medications.
- Medications or food that may inhibit iron absorption.
- Dietary information to increase oral iron intake provide written instructions to the woman about iron supplementation.

At each antenatal visit:

- Assess and document the woman for compliance with taking the medication.
- Assess and document side-effects from the medication. Provide advice for management of any side-effects.
- Assess compliance to dietary recommendation.

Dietary Intake

Sources of dietary iron include meat, poultry and fish which are two to three times more absorbable than plant-based iron foods and iron-fortified foods. Meat, poultry and fish increase absorption of iron,8 and ascorbic acid provides an enhancing effect on absorption[37]. Orange juice is often recommended in pregnancy, although some iron supplement contain Vitamin C. Vegetarians should be encouraged to eat foods high in iron, such as, tofu, beans, lentils, spinach, whole wheat breads, peas, dried apricots, prunes and raisins [37]. Foods or medications that interact or inhibit iron absorption.

Medications inhibiting absorption or contraindicated include:

- Anticonvulsants
- Sulphonamides
- Medications that raise gastric pH e.g. antacids
- Dietary inhibitors may include as

- Calcium in dairy products e.g. cheese
- Tea and coffee [37]
- Chocolate
- Spinach and beetroot, soy products 10 phytates (salts found in plants capable of forming insoluble complexes with iron) e.g. bran, cereal.18 Non-haem iron requires an acidic pH to be reduced to ferrous for gut absorption. A gap of 2 hours from dietary or medication inhibitors of iron absorption appears to be sufficient to avoid the problem.

Side-effects of oral medications and management:

When oral liquid iron is used it should be diluted with water and a straw used to prevent discolouration of the teeth. However, liquid iron supplements should be checked for the content of elemental iron. Side-effects of oral iron supplements include nausea, epigastric pain, constipation and black discolouration of the faeces [38].

Management for side effects include

Response to therapy is feeling of well, improved look and better appetite. Haematologically, there is reticulocyte response in 5-10 days with a rise in Hb concentration from 0.3 g to 1.0 g per week and haematocrit subsequently. If there is no significant clinical or haematological improvement within 3 weeks, diagnostic re-evaluation is needed. Reasons of failure to respond to oral therapy are inaccurate diagnosis (non-iron) deficiency microcytic anemia, such as thalassaemia, pyridoxine deficiency and lead poisoning), non-compliance, continuous loss of blood through hook worm infestation or bleeding haemorrhoids, co-existing infection, faulty iron absorption and concomitant folate deficiency.

CONCLUSION

Nutritional deficiency anemia during pregnancy continues to be a major health problem all over the world. To eradicate it certain steps can be taken at individual and community level like education of the women as regards anemia, its causes and health implication. Imparting nutritional education, with special emphasis on strategies based on locally available food stuffs to improve the dietary intake of proteins and iron, administration of appropriate iron supplements and ensuring maximum compliance, deworming, treatment of chronic disease like malaria and universal antenatal care to pregnant women will help in combating this serious problem. Long term policies by government, non-government agencies and the community can be directed to formulate effective plans like eradicating anemia in pregnant women and adolescent girls.

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