



## International Journal of Case Reports (ISSN:2572-8776)



# The multifactorial etiology and approach to iron deficiency anemia in adolescent girls

Lopes, Lisa<sup>1</sup>; Verlooy, Joris<sup>2</sup>; Norga, Koen<sup>2</sup>; van Heerden, Jaques<sup>2</sup>

<sup>1</sup>Department of Pediatrics, Antwerp University Hospital, University of Antwerp, Belgium.

<sup>2</sup>Pediatric Hematology and Oncology, Antwerp University Hospital, University of Antwerp, Belgium.

### ABSTRACT

Iron deficiency anemia (IDA) is a common but underdiagnosed cause of morbidity in adolescent females. Associated thrombocytopenia is rare, but resolves when the anemia is treated with iron supplementation. Menorrhagia is an important cause in the multifactorial etiology and may be familial. This article presents a case of severe anemia and thrombocytopenia in the presence of iron deficiency due to menorrhagia. A holistic approach to IDA is discussed with an approach to the management thereof in adolescent females.

**Keywords:** Iron deficiency, anemia, adolescent, females

### \*Correspondence to Author:

Dr Lisa Lopes

Department of Pediatrics, University Hospital of Antwerp, Wilrijkstraat 10, Edegem, 2650, Belgium.

### How to cite this article:

Lopes, Lisa; Verlooy, Joris; Norga, Koen; van Heerden, Jaques. The multifactorial etiology and approach to iron deficiency anemia in adolescent girls. International Journal of Case Reports, 2020 4:130

 eSciPub  
eSciPub LLC, Houston, TX USA.  
Website: <https://escipub.com/>

## Introduction

Iron deficiency anemia (IDA) is a common but underdiagnosed cause of morbidity in adolescent females<sup>1,2,3</sup>. There are several factors that increase the risk in this subpopulation<sup>3,4,5</sup>. Thrombocytopenia is a rare and often forgotten complication of iron deficiency<sup>6-8</sup> and the pathophysiology thereof is not fully understood<sup>8,9,10</sup>. Yet here is an important association between menorrhagia, thrombocytopenia and iron deficiency<sup>6,11</sup>. This article presents a case of severe anemia and thrombocytopenia in the presence of iron deficiency due to menorrhagia. Genetic causes of IDA and an approach to the management thereof in adolescent females are discussed<sup>12</sup>.

## Case:

A 15-year-old asymptomatic adolescent female with an uneventful medical and surgical history presented with a coincidental finding of anemia and thrombocytopenia during a general consultation. On inquiry, the 15-year-old patient had no medical history of note, but suffered from menorrhagia. She followed a balanced, iron-rich diet.

Clinically she patient was pale with an asymptomatic anemia and a normal nutritional status. Signs of bleeding were ruled out and there were no clinical arguments for malignancy such as hepatosplenomegaly or lymphadenopathy.

Her 13-year-old younger sister, already in treatment for anemia and menorrhagia, was the primary patient during the consultation and showed symptoms of fatigue. Their mother had received blood transfusions in adolescence due to anemia and confirmed high menstrual blood volumes.

A microcytic anemia of 6.7 g/dL, normal reticulocytes and thrombocytopenia with  $92 \times 10^9$  platelets/L were confirmed in the 15-year-old patient. A low iron status and reserve were identified with iron of 12 µg/dL, total iron binding capacity (TIBC) of 51 µg/dL, a calculated iron saturation of 2% and ferritin of 2 µg/dL. Normal

liver function, kidney function, thyroid function and clotting profile were confirmed. Hemolysis, cytomegalovirus, Epstein Barr virus and Parvovirus were ruled out. Furthermore, other causes of anemia and thrombocytopenia, such as auto-immune and oncological diseases, were ruled out by screening on blood tests and flowcytometry. No abnormalities were found upon gynecological consultation.

Blood values at menarche showed a normal blood count with a normal hemoglobin of 12.5 g/dL and a normal number of platelets of  $208 \times 10^9$ /L.

The diagnosis of IDA with thrombocytopenia due to primary menorrhagia was made. There was a clear familial component with a younger sister and mother having similar medical histories without exclusion of Von Willebrand's disease.

Oral iron supplementation, optimization of diet and oral contraception for menstrual regulation were started. At a two-week follow-up, the hemoglobin had decreased (see Figure 1). A red cell transfusion was administered for symptomatic anemia, which included tachycardia and fatigue. At 6 weeks after diagnosis the anemia, thrombocytopenia and iron deficiency had resolved.

## Discussion:

Iron deficiency anemia is a well-known disease with a significant impact on the quality of a patient's life<sup>4</sup>.

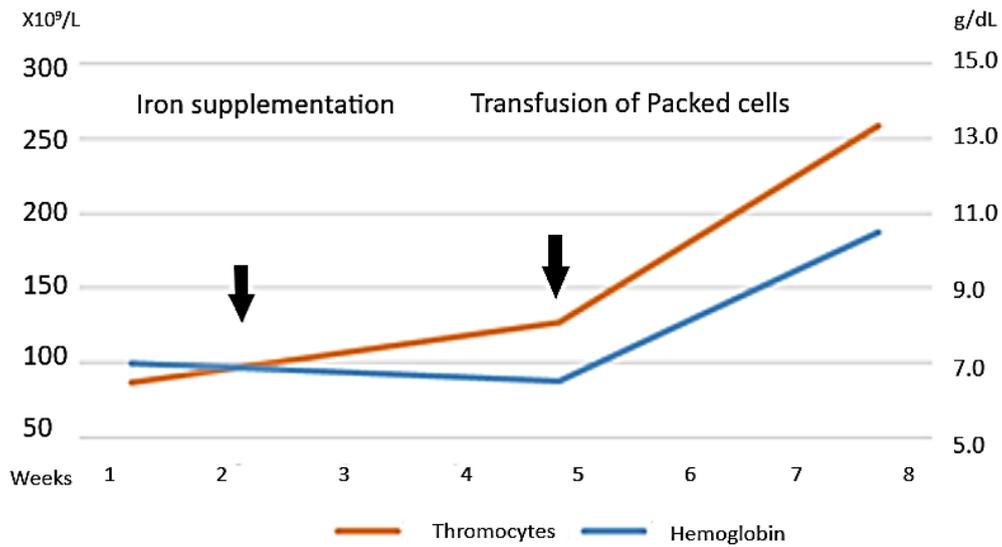
## Epidemiology

Worldwide, in children and adolescents, IDA is one of the leading causes of "years lived with disability"<sup>1</sup>. In 2013 there were 600 million cases diagnosed<sup>1</sup>. The prevalence is 30% to 48% in developing countries – in comparison with 4.3% to 20% in developed countries – mainly due to malnutrition<sup>2</sup>. Prevalence rates in adolescents are not well documented, but have been reported to be 9% in females 12–15 years and 15% in females between 16 and 19 years of age<sup>2</sup>.

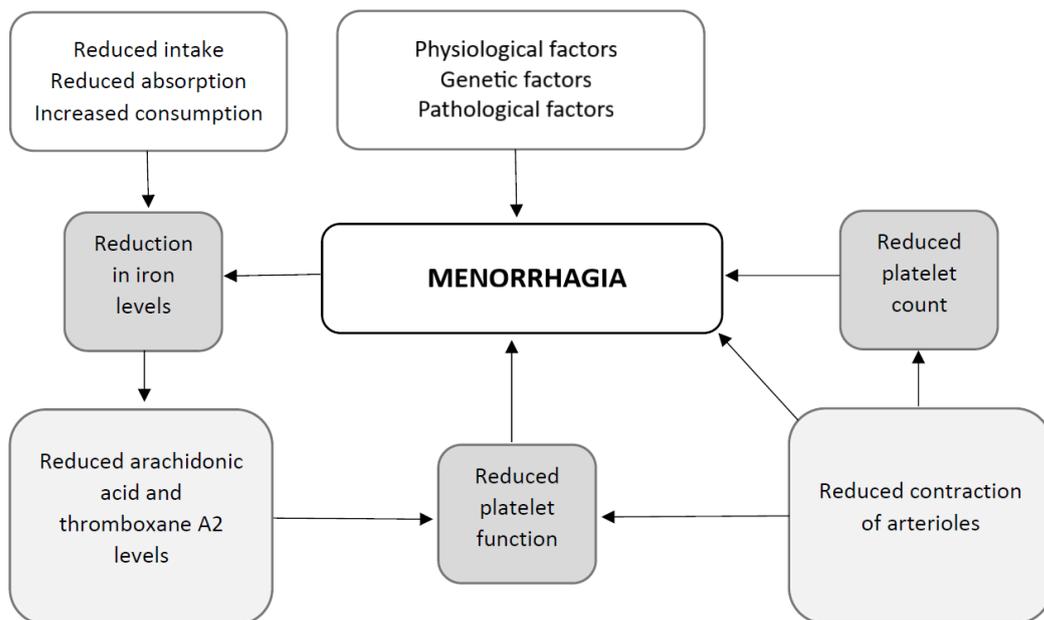
## Risk factors and etiology

Adolescent women are at an increased risk of developing iron deficiency and subsequent anemia <sup>1,2,12,13</sup>. The etiological factors are interlinked <sup>14</sup>. There is an increased iron need during adolescence caused by rapid growth and muscle development <sup>14</sup>. A combined insufficient intake of iron due to a change in eating habits, eating disorders and increased carbohydrate-

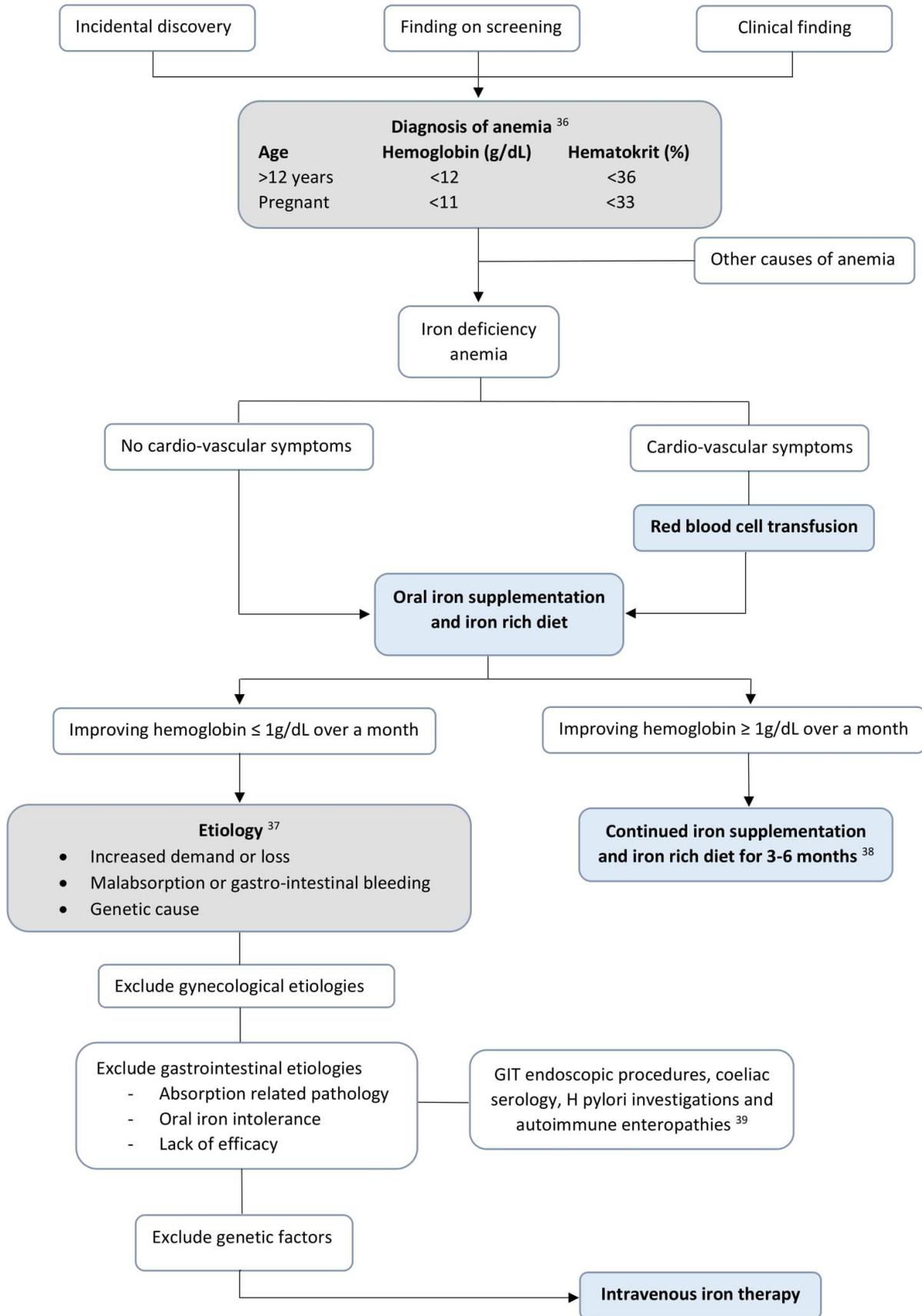
rich diet or fast-food intake, in an age group at higher risk for dietary variability, increases the deficiency <sup>5,14</sup>. The prevalence of obesity therefore increases in children and adolescents <sup>14</sup>. Iron deficiency can be associated with a fat-rich diet and low iron content, compounded by a continuous inflammatory state associated with obesity <sup>4</sup>.



**Figure 1: The thrombocyte and hemoglobin count during management of the case.** The evolution of thrombocyte counts (X10<sup>9</sup>/L, left Y-axis) and hemoglobin level (g/dL, right Y-axis) over 8 weeks (X-axis) after start of iron suppletion and a packed red blood cell transfusion



**Figure 2: The pathophysiology of thrombocytopenia during menorrhagia**



**Figure 3: An approach to anaemia with IDA and thrombocytopenia in an adolescent female**

Excessive or severe menstrual blood loss is an important cause of iron deficiency<sup>15</sup>. It occurs in up to 40% of adolescents<sup>15</sup>. Of these, up to 20% would have an underlying bleeding disorder<sup>16</sup>. Adolescents participating in endurance sports are at an increased risk of developing IDA. Insufficient dietary iron intake, physiological hemolysis, sweating and mild exercise induced inflammation contribute to IDA<sup>3,4</sup>.

### **Pathophysiology of iron deficiency and thrombocytopenia**

IDA is accompanied by a normal or increased platelet count<sup>17</sup>. In rare cases it can lead to thrombocytopenia<sup>6,7,8</sup>. The exact mechanism is not completely clear, yet the platelet count rapidly improves with iron supplementation, confirming that iron is an important component in platelet production<sup>6,7,8</sup>.

In cases of IDA where bone marrow aspirates were done, no signs of erythroid hyperplasia were found, but increased megakaryocytes were present<sup>8</sup>. This disproves the postulation that stem cell competition is responsible for the thrombocytopenia. A more plausible explanation can be found in the double compartment model of an “inhibitor” compartment and an “essential” compartment<sup>10</sup>. In the “inhibitor” compartment, iron acts as an inhibitor so that the platelet count does not rise above a certain limit<sup>10</sup>. This can explain a reactive thrombocytosis in IDA<sup>10</sup>. The “essential” compartment requires iron for the production of platelets<sup>10</sup>. When iron deficiency occurs, the “inhibitor” compartment is affected first<sup>12</sup>. This leads to thrombocytosis<sup>10</sup>. Thrombocytopenia occurs when the iron deficiency is severe enough to affect the “essential” compartment<sup>10</sup>. A second study determined the regulating role of iron on the platelet number by determining the iron concentration in platelets to be approximately 12.28 µg/g<sup>18</sup>.

The clinical presentation of IDA can be due to three main interacting factors (see Figure 2): menorrhagia, thrombocytopenia and iron deficiency<sup>6,19</sup>. Menorrhagia leads to iron loss and consumption of platelets. In addition, iron

deficiency reduces platelet aggregation<sup>20,21</sup>. Iron produces free oxygen radicals that ensure the removal of arachidonic acid and thromboxane A2 from the phospholipids of the platelets<sup>20</sup>. There is also evidence that iron chelators would inhibit platelet aggregation, production of thromboxane and lipoxygenase activity<sup>21</sup>. This can in turn worsen the menorrhagia. Furthermore, a qualitative and quantitative platelet dysfunction can be caused by menorrhagia due to inadequate contraction of arterioles of the endometrium<sup>22</sup>.

### **Genetic and inherited factors**

Hereditary iron-refractory iron deficiency anemia (IRIDA) is an autosomal recessive anemia associated with impaired iron absorption and utilization<sup>23,24</sup>. The disease is completely resistant to oral and partial intravenous iron absorption due to a defect in the Tmprss6 gene that encodes for Matriptase-2<sup>23,24</sup>. To date 40 different genetic defects have been described<sup>23</sup>, but little is known about the exact pathophysiology and the genotype-phenotype correlation<sup>24</sup>. This protein is a down regulator of hepcidin<sup>23,24</sup>, an acute phase reactant that regulates the iron absorption according to the body’s iron status<sup>4</sup>. When the amount of iron is decreased, the expression of hepcidin will also decrease, thereby improving iron uptake and the removal of iron from tissue reserves<sup>3</sup>. In IRIDA, hepcidin will be relatively high compared to the iron content<sup>23,24</sup>. Due to higher hepcidin, iron absorption is less effective via oral iron substitution<sup>24,25</sup>. There are also differences between the degree of responsiveness compared to oral iron substitution within the same genotype<sup>23</sup>. The prevalence is not known, as the pathology has only recently been described and has possibly been underdiagnosed<sup>25</sup>. In this case, further genetic studies were not indicated because of the adequate response to iron supplementation.

Other genetic diseases associated with menorrhagia are Von Willebrand’s disease, platelet function disorders, clotting factor deficiency and hereditary collagen disorders

such as Ehlers-Danlos and Benign Joint Hypermobility Syndrome<sup>16</sup>. Idiopathic menorrhagia in itself has been described to be genetically determined<sup>26</sup>.

### Screening and guidelines

Although IDA is a frequent occurrence in adolescent girls, only a limited number of professional organizations incorporate this risk group into standard prevention guidelines<sup>13</sup>. A 2010 report by the Committee on Nutrition of the American Academy of Pediatrics on IDA focused on screening males between birth and three years<sup>27</sup>. It neglected to focus on post-menarche adolescent females as a major group at risk for IDA<sup>27</sup>.

The American College of Obstetrics and Gynecology and the American Academy of Family Physicians recommend hemoglobin screening in pregnant women, but provide limited guidelines on screening in non-pregnant women and girls<sup>28,29</sup>. The US Preventive Services Task Force (USPSTF) did not find enough evidence to screen for anemia in young children or pregnant women and do not provide any guidelines for other populations<sup>30,31</sup>.

In contrast, the American Academy of Pediatrics (AAP) recommends that all adolescents should be evaluated for risk factors for developing iron deficiency, such as extensive menstrual or other blood loss, low iron intake or a previous diagnosis of IDA<sup>32</sup>. In the case of positive screening the AAP suggests biochemical analysis to determine the cause<sup>32</sup>.

The Center of Disease Control and Prevention (CDC) advocates for screening all non-pregnant women from fertile age, starting from adolescence, by means of a hemoglobin and hematocrit test every five to ten years<sup>33</sup>. Annual screening is recommended in women at high risk for iron deficiency with severe menstrual blood loss or bleeding tendencies<sup>33</sup>. The National Institute for Health and Care Excellence (NICE) guidelines recommend a complete blood count for the screening of women with a history of menorrhagia<sup>34</sup>. Even then a number of cases of

IDA will be missed, as a reduction in hemoglobin follows a decrease in ferritin<sup>4</sup>.

Therefore, further discussion is needed to provide comprehensive guidelines for screening and diagnosing IDA in adolescent girls.

### Management:

As IDA in female adolescents is multifactorial, the approach should also consider multiple aspects<sup>4</sup> (see Figure 3).

Iron deficiency and IDA are chronic conditions and can often go undetected for long periods due to non-specific symptomatology<sup>4</sup>. Diagnosis of anemia is therefore often coincidental with blood analysis for other reasons. When symptoms such as fatigue, poor concentration, tachycardia and paleness are present, anemia should be high on the differential list of causes<sup>4</sup>. As recommended by the AAP and CDC, standard screening should take place in specific age groups and patients at risk<sup>32-33</sup>.

After diagnosis of anemia it is important to rule out severe causes of anemia, especially if other cell lines are simultaneously affected<sup>35,36</sup>. If an iron deficiency is confirmed, an etiology should be identified. A thorough medical history with attention to nutritional habits, menstrual pattern, family and personal medical history as well as medication usage must be explored<sup>3</sup>. The medical examination must focus on identifying pathology in organ systems important to the production of blood components and acquiring the building blocks of blood, such as the gastrointestinal and hemopoietic system<sup>3</sup>. This includes gastrointestinal causes of malabsorption and blood loss in, for example, celiac disease, gastritis, IBD, hepatic diseases and bone marrow pathology<sup>3</sup>.

Often the cause is multifactorial, and therefore the management should be as well. First of all a distinction should be made between symptomatic and asymptomatic anemia to evaluate if a red cell transfusion is indicated<sup>3,37</sup>. Then the iron repletion therapy should be started<sup>3,37</sup>. The three routes include oral iron substitution, parenteral iron or red cell

transfusion<sup>3,37</sup>. The latter is reserved for severe anemia with cardiovascular signs and/or symptoms<sup>3,37</sup>.

Oral treatment is preferred in stable patients. This is an efficient, inexpensive and safe method<sup>3,37</sup>. Intravenous iron administration is indicated with failed oral therapy, intolerance to oral iron, need for rapid iron repletion, chronic diseases with increased need or loss of iron, and in the presence of intestinal absorption pathologies<sup>3,37</sup>.

Consideration of any underlying pathological causes is important. For example, in the case of suspected severe menstrual blood loss, gynecological advice should be sought for hormonal intervention and uterine anatomical malformations should be ruled out<sup>4</sup>.

All these measures should be taken in conjunction with an iron-rich diet to increase the dietary intake of iron as well as to optimize body composition<sup>5</sup>.

The long-term management depends on the severity of the anemia. In mild anemia, a first control blood sample is sufficient four weeks after the start of treatment<sup>38</sup>. Generally hemoglobin will rise by 1–2 g/dL during this period<sup>17,37</sup>. In cases of more severe anemia, more vigilant follow-up should be planned to confirm the diagnosis and screen for complications<sup>37</sup>. The first signs of therapeutic success can appear within 48 to 96 hours after the start of iron substitution, as reticulocytosis will appear<sup>37</sup>. Hemoglobin will also start to increase at a rate of 0.1–0.4 g/dL per day<sup>17</sup>. After normalization of blood values, iron substitution should be continued for two to three months<sup>17,37</sup>.

Failure of oral iron substitution can signal various causes, such as non-compliance, erroneous dosing, inadequate absorption (for example IBD or celiac disease), concurrent infection or inflammation, and the presence of a vitamin B12 or folic acid deficiency<sup>37</sup>. Screening should be done for continued blood losses in cases with occult gastrointestinal losses or untreated

menorrhagia<sup>37,39</sup>. Re-evaluation should always be done to confirm the accuracy of the diagnosis<sup>37</sup>. In the absence of these factors and with unsatisfactory response to treatment, intravenous therapy can be considered<sup>37</sup>.

## Conclusion

A timely diagnosis of IDA in female adolescents is important. However, IDA is often an unrecognized problem in this population. This case demonstrates that iron deficiency can cause both anemia and thrombocytopenia and highlights the risk factors in this population group for the development of IDA. It is advisable to consider family history and to rule out more severe disorders. Iron substitution is not the only management aspect in IDA. Rather, it is important to adopt a holistic approach and to address the underlying risk factors and causes.

## References

- 1 Vos T *et al.* Global and national burden of diseases and injuries among children and adolescents between 1990 and 2013 findings from the global burden of disease 2013 study. *JAMA Pediatr* 2016;170(3):267-87.
- 2 Gergerding J *et al.* Iron deficiency – United States, 1999–2000. *MMWR. Morb Mortal Wkly Rep* 2002;51(40):897-901.
- 3 Camaschella C. Iron-deficiency anemia. *N Engl J Med* 2015; 372:1832–43.
- 4 Percy L, Mansour D, Fraser I. Iron deficiency and iron deficiency anaemia in women. *Best Pract Res Clin Obstet Gynaecol* 2017; 40:55-67.
- 5 De Andrade Cairo RC, Rodrigues Silva L, Carneiro Bustani N, Ferreira Marques CD. Iron deficiency anemia in adolescents: A literature review. *Nutr Hosp* 2014 ;29(6):1240-9.
- 6 Ibrahim R *et al.* Triad of iron deficiency anemia, severe thrombocytopenia and menorrhagia: A case report and literature review. *Clin Med Insights Case Rep* 2012; 5:23-7
- 7 Morris VK, Spraker HL, Howard SC, Ware RE, Reiss UM. Severe thrombocytopenia with iron deficiency anemia. *Pediatr Hematol Oncol* 2010;27(5):413-9.
- 8 Perlman MK, Schwab JG, Nachman JB, Rubin CM. Thrombocytopenia in children with severe iron deficiency. *J Pediatr Hematol*

- Oncol* 2002;24(5):380-4.
- 9 McDonald TP, Clift RE, Cottrell MB. Large, chronic doses of erythropoietin cause thrombocytopenia in mice. *Blood* 1992; ;80(2):352-8.
  - 10 Karpatkin S, Garg SK, Freedman ML. Role of iron as a regulator of thrombopoiesis. *Am J Med* 1974; ;57(4):521-5.
  - 11 Berger M, Brass L. Severe thrombocytopenia in iron deficiency anemia. *Am J Hematol* 1987; 24(4):425–8.
  - 12 Powers JM, Stanek JR, Srivaths L, Haamid FW, O'Brien SH. Hematologic considerations and management of adolescent girls with heavy menstrual bleeding and anemia in US children's hospitals. *J Pediatr Adolesc Gynecol* 2018; ;31(5):446-450.
  - 13 Cooke AG, McCavit TL, Buchanan GR, Powers JM. Iron deficiency anemia in adolescents who present with heavy menstrual bleeding. *J Pediatr Adolesc Gynecol* 2017;30(2):247-250.
  - 14 Mesías M, Seiquer I, Navarro MP. Iron nutrition in adolescence. *Crit Rev Food Sci Nutr* 2013;53(11):1226-37.
  - 15 Friberg B, Kristin Örnö A, Lindgren A, Lethagen S. Bleeding disorders among young women: A population-based prevalence study. *Acta Obstet Gynecol Scand* 2006; ;85(2):200-6.
  - 16 Haamid F, Sass AE, Dietrich JE. Heavy menstrual bleeding in adolescents. *J Pediatr Adolesc Gynecol* 2017; ;30(3):335-340.
  - 17 Kasper CK, Whissell DYE, Wallerstein RO. Clinical aspects of iron deficiency. *JAMA J Am Med Assoc* 1965; ;191(5):359-363.
  - 18 Kiem J *et al.* Elemental composition of platelets. Part II. Water content of normal human platelets and measurements of their concentrations of Cu, Fe, K, and Zn by neutron activation analysis. *Clin Chem* 1979; ;25(5):705-10.
  - 19 Verma V *et al.* An analysis of the relationship between severe iron deficiency anemia and thrombocytopenia. *Ann Hematol* 2015; 94:535-7.
  - 20 Polette A, Blache D. Effect of vitamin E on acute iron load-potentiated aggregation, secretion, calcium uptake and thromboxane biosynthesis in rat platelets. *Atherosclerosis* 1992;96(2-3):171-9.
  - 21 Barradas MA, Jeremy JY, Kontoghiorghes GJ, Mikhailidis DP, Hoffbrand AV, Dandona P. Iron chelators inhibit human platelet aggregation, thromboxane A2 synthesis and lipoxygenase activity. *FEBS Lett* 1989; ;245(1-2):105-9.
  - 22 Taymor ML, Sturgis SH, Yahia C. The etiological role of chronic iron deficiency in production of menorrhagia. *JAMA J Am Med Assoc* 1964 ;187:323-7.
  - 23 De Falco L *et al.* Review articles: Iron refractory iron deficiency anemia. *Haematologica* 2013; 98(6):845–53.
  - 24 Donker AE *et al.* Iron refractory iron deficiency anemia: A heterogeneous disease that is not always iron refractory. *Am J Hematol* 2016;91(12): E482-E490.
  - 25 Donker AE *et al.* Practice guidelines for the diagnosis and management of microcytic anemias due to genetic disorders of iron metabolism or heme synthesis. *Blood* 2014;123(25):3873-86.
  - 26 Kuzmina N, Palmblad J, Mints M. Predictive factors for the occurrence of idiopathic menorrhagia: Evidence for a hereditary trait. *Mol Med Rep* 2011; ;4(5):935-9.
  - 27 Baker RD *et al.* Clinical report: Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). *Pediatrics* 2010;126(5):1040-50.
  - 28 The American Obstetrics and Gynecologists. ACOG practice bulletin no. 95: Anemia in pregnancy. *Obstet Gynecol* 2008; 112(1):201.
  - 29 Short MW, Domagalski JE. Iron deficiency anemia: Evaluation and management. *Am Fam Physician* 2013;87(2):98-104.
  - 30 Siu AL. Screening for iron deficiency anemia in young children: USPSTF recommendation statement. *Pediatrics* 2015;136(4):746-52.
  - 31 McDonagh MS, Blazina I, Dana T, Cantor A, Bougatsos C, Screening and routine supplementation for iron deficiency anemia: A systematic review. *Pediatrics* 2015;135(4):723-33.
  - 32 American Academy of Pediatrics. Adolescence visits. In: *Bright futures: Guidelines for health supervision of infants, children, and adolescents*, 2017. <https://brightfutures.aap.org>. Accessed June 2019.
  - 33 Broome C, et al. Recommendations to prevent and control iron deficiency in the United States: Centers for Disease Control and Prevention. *MMWR Recomm Rep* 1998.

- 34 National Institute for Health and Care Excellence. Heavy menstrual bleeding: Assessment and management. *Clin Guidel* 2007.
- 35 Orkin S. *Nathan and Oski's hematology and oncology of infancy and childhood*, 8th ed. Philadelphia, 2015.
- 36 World Health Organisation. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. [www.who.org](http://www.who.org) Accessed October 2019.
- 37 Pasricha SRS *et al.* Diagnosis and management of iron deficiency anaemia: A clinical update. *Med J Aust* 2010;193(9):525-532.
- 38 Sills R, Iron-deficiency Anemia, Part XXI, Diseases of the blood, Ch455, p2323, Nelson's textbook of pediatrics (20th edn.), by R. Kliegman, B. Stanton, J. St. Geme, N. Schor (eds), Elsevier, Philadelphia, 2016.
- 39 Stein, J., Hartmann, F. & Dignass, A. Diagnosis and management of iron deficiency anemia in patients with IBD. *Nat Rev Gastroenterol Hepatol* 2010; 7(11):599–610.

