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ORIGINAL ARTICLE

Iron deficiency in pregnancy: an Italian Survey

Running title: Iron deficiency and pregnancy

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ABSTRACT

Objective. Iron deficiency with (IDA) or without anemia (IDWA) represents a global health issue. The present paper aims to evaluate several skills concerning the prevention of IDWA and the appropriate management of IDA, in pregnancy and in the post-partum, testing a heterogeneous group of Italian obstetricians.

Materials and Methods. On April 2022, a group of obstetricians of Lazio region (GOAL Working Group) promoted an online survey among its members based on 27 questions dealing with IDA and IDWA in pregnancy and in the post-partum; aspects related to the Patient Blood Management (PBM) have also been investigated.

Results. About 30% of the GOAL members answered the questionnaire. The prevalence of IDWA is thought to be around 41%, leading to a higher risk of adverse pregnancy outcomes. 54.1% of responders evaluate iron storage at the first visit in pregnancy thus proposing a diet rich in iron to all women they follow (67.2%). Although iron administration is more often needed to correct hemoglobin levels before starting labour, the prevalence of blood transfusion in the post-partum is thought to be around 2-5% (50.8%). Only the half of responders knows the PBM approach.

Conclusions. It is desired to define how clinicians who care for pregnants perceive, frame and treat IDA and IDWA, which are too often not promptly diagnosed and managed, in order to improve antenatal care.

Key words: iron deficiency, iron deficiency anemia, pregnancy, iron treatment

Introduction

Worldwide approximately one-third of the population is anemic. In hospitalized patients, the prevalence of anemia is approximatively 25-50% percent, depending on comorbidities and demographic factors (e.g. age, gender), and increases within the processes of care (e.g. procedural blood loss and phlebotomies) [1]. Anemia has been recognized as an independent risk factor for adverse outcome including higher risk of hospitalization or readmission, prolonged hospital stay, morbidity and mortality [2,3], as well as additional costs to the health care system [4]. The most common of anemia is represented by iron lack. During pregnancy and the post-partum, iron deficiency anemia (IDA) and iron deficiency without anemia (IDWA) represent global health issues thus involving over 40% of women [5], leading to an increased risk of adverse maternal and/or perinatal outcomes (e.g. reduced physical activity, cognitive performance status and immune function as well as tiredness and increased depressive episodes, for the mother; preterm birth, fetal growth restriction, intrauterine fetal death, low Apgar scores and neonatal infection, for the baby). Such risks arise from the pivotal role of iron to several biologic functions (e.g. respiration, energy production, DNA synthesis and cell proliferation) [6-8]. The human body is able

to store iron thanks to different pathways, including the recycling of martial storages after the breakdown of red cells and the retention of iron in the absence of an excretion mechanism. IDWA refers to the reduction of iron stores precedes overt IDA or persists without progression; symptoms of IDWA are basically the same found in patients with IDA. The diagnostic approach includes the evaluation of blood cell count, serum ferritin, serum iron, transferrin (or total iron binding capacity) and transferrin saturation (or saturated iron binding capacity) (TSAT). The appropriate diagnosis is crucial for an adequate therapeutic approach: when a pathological cause is identified, iron supplementation should be combined to the treatment of the underlying cause. Iron replacement should be done orally as the first choice; subjects who need a rapid correction of anemia as well as those with intolerance or refractoriness to oral therapy, or defective intestinal absorption, benefit from intravenous iron administration; on the contrary, the increase of iron intake through the diet alone is not sufficient to treat documented cases of iron deficiency. Transfusion is recommended when clinically indicated. For this reason, the World Health Organization (WHO) promoted an approach called Patient Blood Management (PBM), which is defined as “the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcome” by the Society for the Advancement of Blood Management (SABM) (available at: http://www.sabm.org/). However, questions are raised about the development of knowledge on iron metabolism and available therapies. Being the appropriate management of IDA and IDWA desired for both maternal and newborn health, the present paper aims at evaluating several clinical skills concerning the management of such conditions during pregnancy and the post-partum, testing a heterogeneous group of Italian obstetricians.

Materials and Methods

On April 2022, an Italian group of obstetricians of Lazio region (the so-called GOAL Working Group) promoted an online survey among its members (about 200) based on a smart list of 27 questions dealing with the importance of iron stores and iron deficiency, the management of IDA and IDWA, as well as on the use of the Patient Blood Management (PBM), during pregnancy and the post-partum.

The survey design involved the following steps:

1. The creation of a working group dedicated to carrying out the survey
2. The review of the available Literature
3. The drafting of the survey
4. The collection of an informed consent
5. The submission of the survey to the GOAL Working Group members
6. A reminder 15 days after the submission

The list of the questions is reported in Table 1; the first two investigate clinicians’ experience (years of clinical practice and number of annual births in the hospitals where they work) while the other ones deal with several clinical skills about IDA and IDWA (e.g. prevention, diagnosis, management, outcome and follow up). The results of the online survey, based on the independent opinions and personal experiences of the members who answered the questionnaire, have been reported in this manuscript in order to provide an overview on the perception of IDA and IDWA, during pregnancy and the post-partum, among clinicians who care for pregnants.

Results

About 30% (60/200) of the GOAL members answered the questionnaire. The clinical experience of the respondents is detailed in Table 2: 57% of them have been working for more than 20 years and 15% of the GOAL members have a clinical experience of 15-20 years. The results of the survey are reported in Table 1. According to physicians' opinions and personal experiences, the prevalence of women who start pregnancy with IDWA is thought to be around 41% while the percentage of those entering labour with an adeguate Hb level is one third of the total. Iron deficiency is considered the most common cause of anemia in pregnancy, in more than the half of cases. Several adverse events (e.g. post-partum anemia, length of hospital stay, infective risk, risk of blood transfusion) are thought to be associated with IDWA in 78.3% of responders. The iron supplementation needed throughout pregnancy is thought to be greater than 1000 mg, in more than one third of clinicians (32.8%). Blood count, serum iron levels, ferritin and transferrin are included in the diagnostic approach in 54.1% of responders. Iron storage is assessed by more than the half of clinicians (54.1%) at the first visit in pregnancy; 67.2% of them proposed a diet rich in iron to all women they follow at the beginning of pregnancy, by means of verbal recommendations (62.3%). Iron therapy is thought to be principally needed to correct Hb levels before starting labour (45.9%); other reasons of martial supplementation are providing adequate iron support to the mother and her fetus (26.2%), and correcting Hb levels and iron stores (18%). The majority of responders (59%) considers oral iron therapy only in pregnants affected by IDA, changing the drug if not well tolerated (57.4%). The main limitation of oral iron therapy is represented by gastrointestinal side effects that negatively impact on patient's compliance (55.7%). 78.4% of responders check the effectiveness of oral iron therapy testing blood count and iron profile 30 days after iron supplementation. The most frequent causes of oral iron therapy discontinuation are poor patient's compliance and hive disorders, in 53.2% and 37.1% of clinicians, respectively. Intravenous iron is more frequently administered during the second and the third trimesters of pregnancy (28.8%). The amount of iron needed is calculated by means of Ganzoni's formula (30.4%); 28.6% of clinicians administer the minimum effective dosage. The main limitations of intravenous iron are represented by logistic problems and risks linked to intravenous injection, in 43.1% and 37.9% of responders, respectively. Red blood cells transfusion is generally required in women who experienced peripartum complications (55%); blood transfusion is thought to be due to the failure or the ineffective management of IDA throughout gestation in 20% of clinicians. In the majority of cases, they ask for a consultation (to the transfusion center or to a hematologist) in patients affected by hemoglobinopaties (45.5%) or in cases who not respond to a well-conducted oral iron therapy (27.1%). Focusing on the post-partum, cases for whom clinicians prescribe oral iron therapy are those with Hb levels lower than 10 g/dL 24–48 hours after delivery; intravenous iron administration is more frequently considered in patients who experienced an acute blood loss during delivery. The prevalence of blood transfusion in the post-partum is thought to be around 2-5% in the half of responders (50.8%). The 57.4% of clinicians know the PBM approach while 42.6% do not. Such approach should be implemented, in routine practice or in cases with Hb levels lower than 9 g/dL for 43.9% and 31.6% of clinicians, respectively.

Discussion

Iron content in a woman's body is normally maintained at about 40 mg/kg, balancing iron absorption by enterocytes in the duodenum, and iron mobilization from liver parenchyma and macrophages. Such processes are regulated by hepcidin, produced by the liver, which binds to a cellular iron export protein called ferroportin, causing its internalization. When hepcidin levels are increased, iron is retained in enterocytes or macrophages while when is decreased, stored iron is mobilized into the circulation [9]. A singleton pregnancy carried to term requires a transfer of 500–800 mg of maternal iron. IDWA represents a global health issue leading to an increased risk of adverse pregnancy outcomes (e.g. premature delivery, low birth weight, and infant death) and impaired cognitive development in early childhood [9,10]. Although the impact cited above, iron deficiency is often under-recognized by health system leaders and clinicians, independently from

their clinical experienced [11,12]. First of all, the definition of a normal hemoglobin (Hb) concentration throughout gestation is controversial and lacks consistency across studies. Ideally, the cut-off values should be derived from studies focused on healthy iron-replete (as well as folate- and vitamin B12-replete) women who had normal singleton gestation and delivery. The WHO (2011) defines anemia in pregnancy as Hb levels less than 11 g/dL and classifies such condition as mild (Hb 10-10.9 g/dL), moderate (Hb 7-9.9 g/dL) and severe (Hb levels less than 7 g/dL), according with Hb levels. There are no WHO recommendations on the use of different cut-off points for each trimester, but it is recognized that during the second trimester of gestation, Hb concentration decreases by approximately 0.5 g/dL. Both the American College of Obstetricians and Gynecologists (ACOG) and the UK guidelines recommend screening for anemia as a surrogate for detecting IDWA. The successful management of IDWA and IDA depends on oral preparations, parenteral infusion, and blood transfusion. Treatment of iron deficiency anemia generally begins with oral supplementation which can lead to gastrointestinal side effects. When the serum ferritin level is higher than 70 µg/L, iron stores are adequate to support pregnancy and no supplementation is given; on the contrary, when serum ferritin is less than 30 µg/L, the patient is treated with 80–100 mg elemental iron/day orally. Iron intravenous administration is indicated when oral iron fails because of compliance/tolerance issues, in subjects affected by comorbidities which may affect iron absorption or ongoing iron losses that exceed absorptive capacity [13,14]. In the last years, several activities (e.g. hospital meetings, internal discussions and congresses) dealing with anemia in pregnancy were conducted in the maternal-fetal medicine units. Being the appropriate management of iron deficiency beneficial and desired for both maternal and newborn health, a key point is to understand how obstetricians manage iron deficiency in their routine practice. Furthermore, to avoid inappropriate practices, the WHO promoted the PBM approach which is a systematic and multidisciplinary approach able to optimize hemostasis, manage anemia, minimize iatrogenic blood loss, and improve tolerance to anemia and outcomes, in both surgical and nonsurgical patients. In Italy, the implementation of the PBM approach is mandatory by law and so, the Lazio region adopted it in both public and private hospitals.

Conclusions

During pregnancy and the post-partum, IDA and IDWA represent global health issues as well as nutrition and lifestyle [15]. IDA and IDWA involve over 40% of women [5], leading to an increased risk of adverse maternal and/or perinatal outcomes. For example, in clinical routine practice gynecologists deal with post-partum hemorrhage management which requires iron/red blood cells administration combined or not with other procedures in order to reduce maternal morbidity and mortality [16]. The present survey summarizes how a heterogeneous group of Italian obstetricians perceives, frames and treats iron anemia in order to improve clinical care.

COMPLIANCE WITH ETHICAL STANDARDS

This study was performed according with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (https://www.equator-network.org/reporting-guidelines/strobe/).

Authors contribution

G.P. Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing; L.A. Conceptualization, Supervision, Validation, Investigation; F.B. Conceptualization, Supervision, Validation, Investigation; F.A.B. Conceptualization, Supervision, Validation, Investigation; M.B. Conceptualization, Supervision, Validation, Investigation; M.B. Conceptualization, Supervision, Validation, Investigation; R.B. Conceptualization, Supervision,

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Disclosure of interests

All Authors declare no financial and/or religious conflict of interest

Informed consent

N/A

Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1. The questionnaire sent to the GOAL Working Group members, and its results (expressed as percentage of responders).

		A	B	C	D	E
1	**How many years have you been practicing?** A. Less than 5 years; B. 5-10 years; C. 10-15 years; D.15-20 years; E. More than 20 years	10%	10%	8%	15%	57%
2	**How many births are carried out every year in the hospital where you work?** A. Less than 1000; B. 1000-2000; C. 2000-3000; D.3000-3500; E. More than 3500	37%	30%	3%	3%	27%
3	**In your experience, how many women present at delivery in accordance with the hemoglobin threshold set by the WHO?** A. Less than 10%; B. 10-30%; C. 30-50%; D.50-70%; E. More than 70%	4%	20%	28%	30%	18%
4	**In your experience, which is the rate of women affected by iron deficiency without anemia (IDWA) in pregnancy?** A. Less than 10%; B. 10-30%; C. 30-50%; D.50-70%; E. More than 70%	6%	33%	41%	15%	5%
5	**In your experience, what is the most common cause of anemia? In what percentage?** A. vitamin b12 deficiency; B. Folic acid deficiency; C. Iron deficiency; D.renal insufficiency; E. Other causes	-	-	100%	-	-

6	**In your experience, what complications do you think may be related to iron deficiency in pregnancy?** A. Postpartum anemia; B. Increase length of hospital stay; C. Increase infective risk; D. increase risk of blood transfusion; E. All	15%	1%	-	5%	79%
7	**What is the average amount of iron needed throughout pregnancy?** A. 100-200; B. 200-500 mg; C. 500-700 mg; D. 700-1000 mg; E. More than 1000 mg	12%	20%	9%	26%	33%
8	**In general, which blood tests do you need for the diagnosis of iron deficiency anemia?** A. blood count and serum iron levels; B. blood count, serum iron levels and ferritin; C. blood count, serum iron levels, ferritin and transferrin; D. hematocrit; E. Other	10%	36%	54%	-	-
9	**In the first trimester, or at the first visit in pregnancy, do you carry out an in-depth study on iron metabolism? If so, in what percentage of cases?** A.Yes; B. No; C. Only in specific cases	54%	44%	2%	-	-
10	**Diet rich in iron: in which cases is it proposed?** A. To all women at the beginning of pregnancy or, in any case, at the first visit; B. In women with hemoglobin level less than 11 g/dL; C. In cases of known food intolerances; D. In vegetarian/vegan women; E. Other cases	67%	28%	2%	2%	1%

11	**Dietary correction: what recommendations?** A. Verbal recommendations; B. Personalized written diet; C. Evaluation of food and drug interactions; D. Information brochure; E. Evaluation of drug interactions	62%	6%	7%	25%	-
12	**What are, in your experience/opinion, the objectives to be pursued when administering martial therapy?** In case of multiple answers, indicate the degree of priority (1,2,3,4,5) A. Start labour with adequate hemoglobin values; B. Correct hemoglobin levels and iron stores (serum ferritin); C. Prevent avoidable transfusion; D. Provide adequate iron support to the mother and her fetus; E. Reduce the risk of blood transfusion	46%	18%	-	26%	10%
13	**Oral iron in pregnancy:** A. to all women, as a prophylaxis; B. the most tolerated, in my experience; C. in low doses, in order to reduce the side effects; D. as a drug, only in the presence of anemia; E. every other day	13%	15%	9%	59%	4%
14	**In your opinion, which is the main limitation of oral iron therapy?** A. Prolonged therapy over time; B.Slow increase of hemoglobin levels; C.Gastrointestinal side effects that reduce compliance; D. Insufficient to support iron demand in late pregnancy; E. Cost to be paid by the patient	10%	16%	57%	10%	7%

15	**You must choose oral iron therapy in an anemic woman:** A. Supplement, to then get to the drug; B. Drug with a possible subsequent change; C. A proper diet is usually sufficient; D. A multivitamin is usually sufficient; E. Other	34%	57%	9%	-	-
16	**How do you check the effectiveness of oral iron therapy?** A. Blood count and iron profile after 15 days; B. Blood count and iron profile after 30 days; C. Hemoglobin and serum ferritin levels; D. I change the therapy in case of further drop in hemoglobin values; E. There is no re-evaluation in pre-established times	13%	74%	7%	3%	3%
17	**In your clinical practice, which are the most frequent causes of discontinuation of oral iron therapy?** A. Hive disorders; B. Lack of clinical efficacy; C. Failure to resolve the symptoms of anemia; D. Poor patient compliance; E. Therapy costs	37%	5%	3%	53%	2%
18	**In which trimester of pregnancy do you administer intravenous iron therapy?** A. Postpartum; B. Second trimester; C. Third trimester; D. Second and third trimesters; E. Never	5%	-	39%	39%	17%

19	**If you administering intravenous iron therapy, how do you determine the amount of iron to be given?** A. Minimum effective dosage; B. By calculation with the Ganzoni formula; C. According to the clinical experience; D. Based on the severity of the symptoms; E. Based on the length of hospital stay	30%	30%	16%	18%	6%
20	**Which are, in your opinion, the main limitations of intravenous iron therapy?** In case of multiple answers, indicate the degree of priority (1,2,3,4,5) A. Logistics; B. Costs; C. Risks linked to intravenous injection; D. Lack in Evidence Based Medicine; E. All	43%	9%	38%	6%	4%
21	**In your experience, which are the causes that most frequently induced a transfusion of red blood cells?** A. Low hemoglobin levels few weeks before delivery; B. Peripartum complications; C.Risk factors; D. Arrival of an anemic woman few days before giving birth; E. Failure or ineffective management of anemia during pregnancy	17%	55%	2%	6%	20%
22	**When do you ask for a consultation (to the transfusion center or to the hematologist)?** In case of multiple answers, indicate the degree of priority (1,2,3,4) A. Low hemoglobin levels; B. Hemoglobinopaties; C. Persistent symptoms; D. Failure to respond to a well-conducted oral iron therapy	12%	46%	15%	27%	-

23	**Postpartum: in which cases do you evaluate a therapeutic support with oral iron therapy?** In case of multiple answers, indicate the degree of priority (1,2,3,4,5) A. Hemoglobin levels < 10 g/dL 24–48 hours postpartum; B. Hemoglobin levels < 11 g/dL one week postpartum; C.Hemoglobin levels < 12 g/dL 8 weeks postpartum; D. Always; E. In case of high blood losses (> 500ml)	85%	-	-	-	15%
24	**Postpartum: in which cases do you evaluate therapeutic support with intravenous iron therapy?** In case of multiple answers, indicate the degree of priority (1,2,3,4,5) A. In case of prepartum known IDA; B. Cesarean section; C. IDWA diagnosis; D. Blood loss greater than 300 ml; E. Acute blood loss during delivery	15%	-	-	-	85%
25	**In your experience, what is the percentage of women transfused in the postpartum?** A. <1%; B. 2-5%; C. 5-7%; D. 7-10%	30%	51%	17%	1%	1%
26	**Do you know the Patient Blood Management?** A.Yes; B.No	58%	42%	-	-	-
27	**Patient Blood Management should be implemented:** A. In cases with hemoglobin levels less than 9 g/dL; B. In cases with coagulation disorders; C. Before a planned surgical intervention; D. In consideration of religious belief (Jehovah's Witnesses) or refusal to transfusion; E. Always	32%	5%	7%	12%	44%

Table 2. Clinical experience of the respondents.

Characteristic	**Frequency (n=60)**
Clinical experience (years):	
- <5	6 (10%)
- 5/10	6 (10%)
- 10/15	5 (8%)
- 15/20	9 (15%)
- >20	34 (57%)
- >45	-