

Review Article

Primary Hereditary Haemochromatosis and Pregnancy

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Background. Haemochromatosis is a rare autosomal genetic disease that can cause multiple organ failure. In the past, this condition was not considered to affect pregnancy. The objectives of this study are to update the management of haemochromatosis in general as there are new treatments being investigated other than phlebotomy and to summarise the effects of the condition on pregnancy and vice versa. **Methods.** The initial search was in Ovid Medline® from 2002 to 2013. Review articles for haemochromatosis and case reports of its related complications in pregnancy were found. None of the reviews addressed pregnancy in detail. A second search in PubMed from 2014 to 2016 included studies regarding haemochromatosis and pregnancy and iron metabolism association with other metals and biomarkers, defining the mechanism of foetomaternal risks in maternal haemochromatosis. A third search at PubMed from 2017 to 2022 using key words haemochromatosis and pregnancy was done to look at the new data. **Results.** The results are qualitative indicating that even in the absence of abnormal iron parameters, haemochromatosis increases the risk of foetomaternal complications due to genetic predisposition, necessitating antenatal monitoring. Newer medications targeting the pathophysiology of the disease to eliminate it are being developed. The coabsorption of lead with iron causes increased risk of maternal preeclampsia, gestational hypertension, foetal congenital abnormalities, and growth problems. There is risk of neurodevelopmental delays, large for gestational age and childhood leukaemia in babies whose mothers and themselves have mutations for haemochromatosis. **Conclusion.** Previously, women with haemochromatosis were thought to have no higher risk of complications than the general population. However, there is evidence of foetomaternal complications. As a result, pregnancy with haemochromatosis necessitates additional monitoring for both mother and baby.

1. Background

Hereditary haemochromatosis (HH) is a genetic condition of iron overload in which increased total body iron stores lead to iron deposition in the liver, heart, pancreas, skin, joints, pituitary gland, and testes, resulting in liver cirrhosis, heart failure, arthritis, diabetes mellitus, skin bronzing, endocrine abnormalities, and skin cancer.

The iron deposition and multiple end-organ damage is gradual due to an inherited predisposition to excessive and inappropriately regulated intestinal iron absorption.

HFE gene mutation was first identified in 1996. The HFE gene has common mutations including C282Y, H63D, and S65C. Rare mutations are V59M, R66C, G93R,

1105T, E168Q, R224G, E277K, V212V, and V295A, called as “private mutations.” The frame shift mutations for HFE include C.340+4T>C, C.1008+1G>A, and C.471del. Therefore, these rare mutations can cause severe clinical disease if they occur as homozygous or as compound heterozygotes with C282Y [1–3].

C282Y has originated by chance in a single Celtic or Viking ancestors in Northwestern Europe 2000 years ago.

In northwest Europe, the incidence of haemochromatosis is 0.5% which is ten times higher than the incidence of cystic fibrosis. The range is from 0% in southern Europe to 12.5% in Ireland. In round figures, the prevalence of the C282Y/C282Y mutation is 1:200 to 1:250 and that of C282Y/H63D is 1:8.

Approximately 95% to 96% of haemochromatosis is due to C282Y homozygosity and 4% is due to C282Y/H63D compound heterozygosity.

The other four common genes after HFE are HAMP (the hepcidin gene), HJV (the hemojuvelin gene), FtR2 (ferritin transport receptor 2 gene), and FPN (ferroportin gene) which are involved in the pathophysiology of hereditary haemochromatosis.

Approximately 19% of clinically characterised hereditary haemochromatosis patients have the disease in the absence of the C282Y mutation, and these are the cases that might be positive for other mutations of HFE or other gene mutations responsible for HH. On a population basis, this contributes to 1% of cases of primary haemochromatosis. Rare mutations and genes other than HFE are tested in research laboratories. Most laboratories only check for C282Y and H63D gene mutations. The tests used are target analysis and sequence analysis. C282Y involves the substitution of the amino acid tyrosine for a cysteine at position 282 whereas H63D involves the substitution of aspartate for histidine at position 63. It is a Mendelian genetic inheritance in which if both parents are heterozygotes, 25% of the children will be affected and 25% will be normal, whereas in homozygote-heterozygote mating, 50% of the children will be affected and 50% will be carriers [2–6].

2. Material and Methods

This is a systematic review, not a meta-analysis. The data for it is qualitative and is given in the form of tables, the titles of which are given at the end of the article under the heading Supplementary Materials (available here) (the tables explaining the characteristics of the studies are uploaded as supplementary files).

The initial search was performed using Ovid Medline® from 2002 to November 2013, and I chose 7 review articles on the topic of haemochromatosis in general, consisting of 848 studies and 3 case reports of complications in the pregnancy and 7 observational studies. None of the reviews addressed pregnancy in detail, and very few case reports indicated serious maternal complications were present in the literature, which is the rationale for writing this review. Another search was performed using PubMed from 2014 to 2016 where 3 review articles including 87 studies and 7 observational studies related to haemochromatosis and pregnancy and iron metabolism associations with other metals and biomarkers were obtained showing maternal and foetal risks in maternal haemochromatosis which have not been mentioned in previous reviews. A third search at the PubMed from 2017 to 2022 found 2 more relevant studies. As a whole, the data included 123 pregnant patients, 2219 mother-infant pairs, and 100973 mother-children pairs among total 498724 patients in observational studies and case reports. See Figure 1 for the search criteria.

2.1. Patient and Public Involvement. There is no patient or public involvement in this review.

3. Results and Discussion

3.1. Section 1 Hereditary Haemochromatosis

3.1.1. Classification of Primary Haemochromatosis [3]

(1) *HFE-Related Haemochromatosis.* Type 1: C282Y/C282Y, C282Y/H63D, H63D/H63D, and other HFE mutations

(2) *Non-HFE Related Haemochromatosis.* Type 2: HJV and HAMP-related haemochromatosis (juvenile haemochromatosis): type 2A: HJV mutation and type 2B: HAMP mutation

Type 3: TfR2 gene mutation-related haemochromatosis

Type 4: FPN gene mutation causing ferroportin disease (classical and nonclassical)

3.1.2. *Pathophysiology of Iron Metabolism.* Iron loss and absorption are in balance, 1 mg per day in men and 1.5 to 2 mg in women. Total body iron in males is 35–45 mg/kg body weight, with a level lower than this for premenopausal females. More than two-thirds of iron is stored in the form of haemoglobin in erythrocytes, with the remainder mostly in the liver. Sloughing of intestinal mucosal cells and menstrual blood loss are the main physiological processes involved in iron loss from the body. In hereditary haemochromatosis, serum iron is high, but iron transport to bone marrow and its use in haemoglobin is not affected so erythropoiesis is not impaired [2]. Excess unbound iron in iron overload generates free oxygen radicals which cause cellular damage [3]. See Figures 2 and 3 for iron metabolism and its regulation by hepcidin.

3.1.3. *Screening.* As said earlier, patients with a negative available genetic test can still have clinical haemochromatosis, while 80% to 90% of individuals with a positive genetic test may never develop iron overload. Disease penetrance is 13.5% for C282Y/C282Y. The cost of serum transferrin saturation and ferritin is 25 dollars each, and the cost of a genetic test ranges between 150 and 500 dollars. Lanktree et al. examined biochemical markers of iron overload in 664 patients referred for HFE gene testing. C282Y homozygosity and C282Y/H63D heterozygosity were found in only 18% of referred patients, and this was the group that had significantly high serum transferrin saturation, serum iron, and haemoglobin. Liver enzymes and ferritin were normal in all the patients [1]. The disease is more severe in relatives of clinically affected C282Y probands than in relatives of probands identified due to elevated serum transferrin saturation, implying higher incidence of cirrhosis, hepatic fibrosis, and arthropathy [4].

Bokhoven et al. stated that C282Y homozygosity and C282Y/H63D heterozygosity have very low clinical penetrance, 2% to 38% in men and 1% to 10% in women, and raised iron parameters are seen in 38–76% of HH patients, but a second added mutation in the HJV or HAMP gene can cause more abnormal and severe iron indices [7].

Target screening should be conducted for diseases that are associated with high prevalence of HFE-C282Y homozygosity like porphyria cutanea tarda (prevalence of HFE,

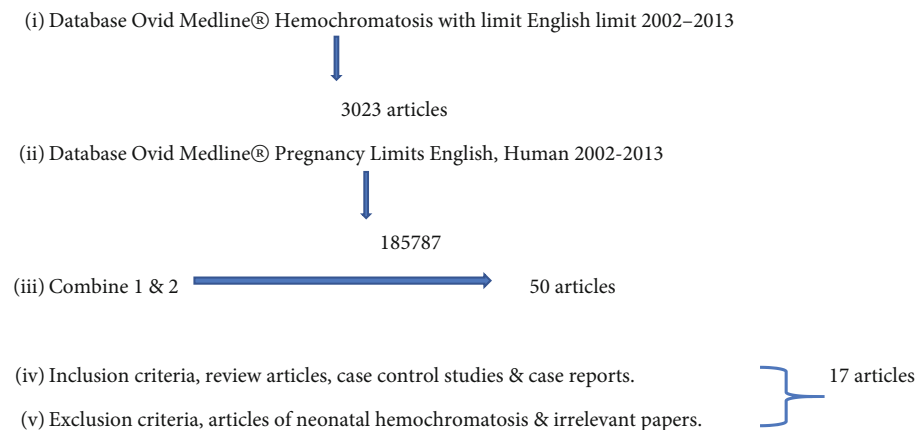
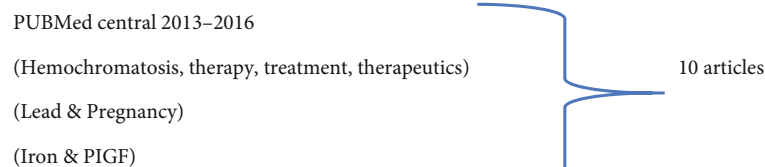
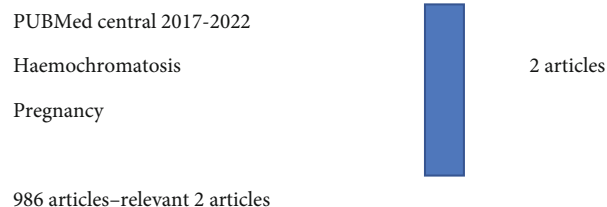
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FIGURE 1: Flow chart search criteria.

5–17%), well-defined chondrocalcinosis, hepatocellular carcinoma (5.4 to 10%), late-onset type 1 diabetes mellitus, unexplained liver disease (3%-5.3%) and raised transferrin saturation, first degree relatives (penetrance was 32%-35% on family-based screening compared to 27%-29% on population based), children from spouses who have HFE homozygosity or heterozygosity, and patients with diabetic retinopathy and nephropathy [5, 6]

If these individuals have high ferritin, the incidence of persistently high serum transferrin saturation is 1% and 0.5%, and 90% of males and 75% of females in this group have C282Y homozygosity [5].

Disease develops after age 40 in HFE hereditary haemochromatosis; however, in juvenile HH, symptoms and signs can develop in third decade of life. Hence, screening in general is advisable after the age 18 years when subjects are able to give informed consent and understand what the implica-

tions are, in terms of psychological effect, insurance, monitoring, and treatment. It is also well known that frequency of phlebotomy is higher in the group who are genetic mutation positive for a given serum ferritin and transferrin saturation.

In conclusion, high prevalence, the existence of sensitive screening tests, significant morbidity and mortality in untreated patients, and effective treatment that improves survival are in favour of population-based screening. However, low clinical penetrance and the disadvantages of detecting asymptomatic people with normal iron parameters which cause social and psychological stress are reasons for targeted screening which is the current practice.

3.1.4. Presentation and Complications. The first symptoms appear between the ages of 30 and 60 years. Disease can present in 4 stages, “genetic mutation with no other abnormality and an increase in serum transferrin saturation,”

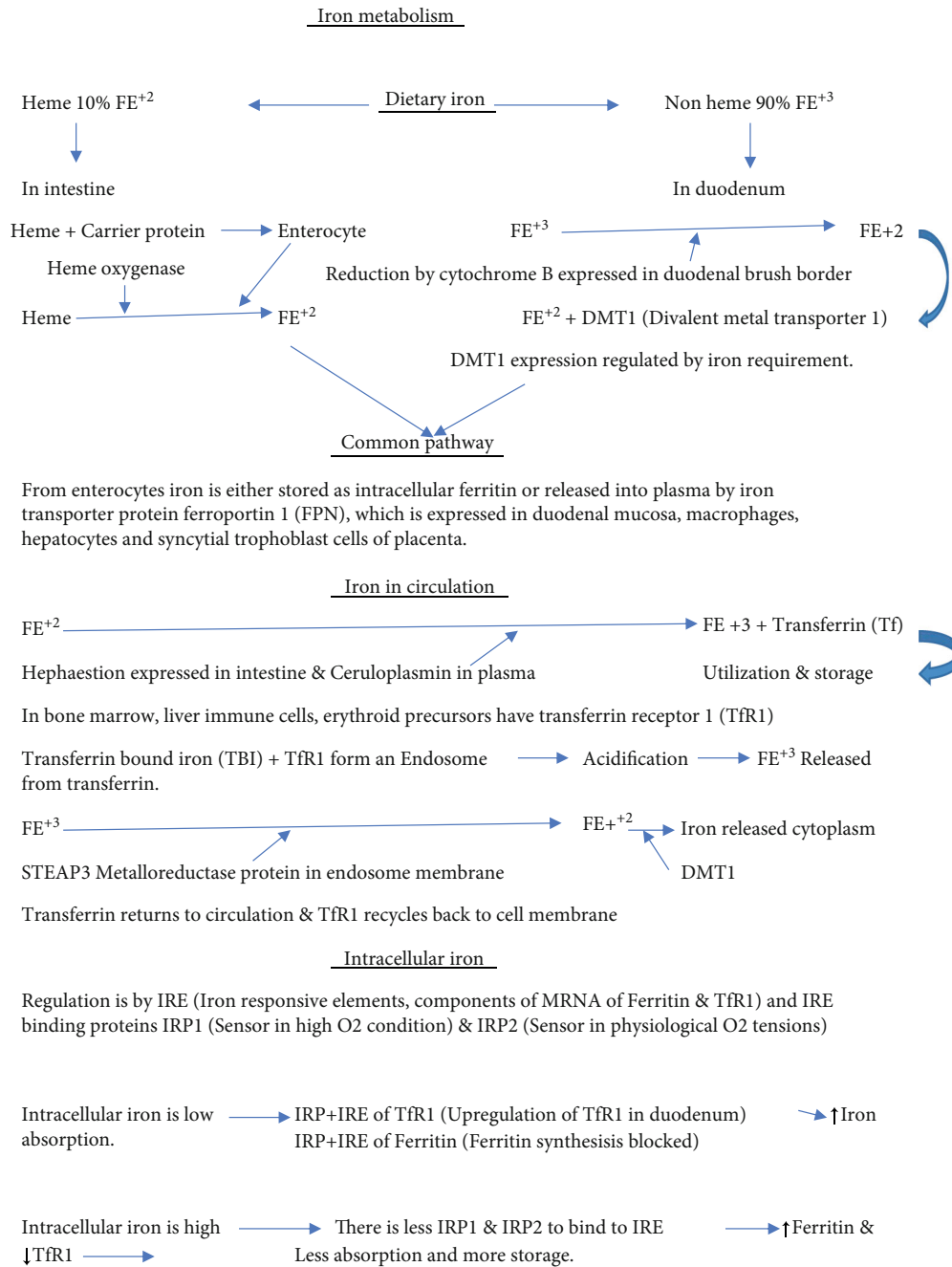


FIGURE 2: Flow chart for iron metabolism [3].

“iron overload of 2-5g but no symptoms,” “iron overload with early symptoms,” and “iron overload with organ damage.” Less than 1% of homozygotes for C282Y have advanced disease.

Cirrhosis is present in 5.8% of homozygous men and 1.9% of homozygous women. Asymptomatic advanced hepatic fibrosis is seen in 25% of cases. For HFE homozygotes, 75% of these have increased serum ferritin and 25% of these with increased serum ferritin also have increased serum collagen peptide confirming that there is significant population of HFE HH who are asymptomatic but have hepatic fibrosis. Among symptomatic patients, 95% have

hepatomegaly. Hepatic cellular carcinoma develops in 5% to 18.5% patients with cirrhosis (RR 200-fold). Cardiomyopathy is both restrictive and dilated. In 3–10% of cases, it is due to iron deposition in the myocardium and/or the conducting bundles. It presents with ECG abnormalities, congestive cardiac failure, cardiac dysrhythmias, and cardiomyopathy. Diabetes mellitus happens in 65% of patients. There is male impotence, erectile dysfunction, a low level of luteinizing hormone, follicle-stimulating hormone and testosterone, and amenorrhea in females due to hypogonadotropic hypogonadism because of pituitary involvement [3, 4].

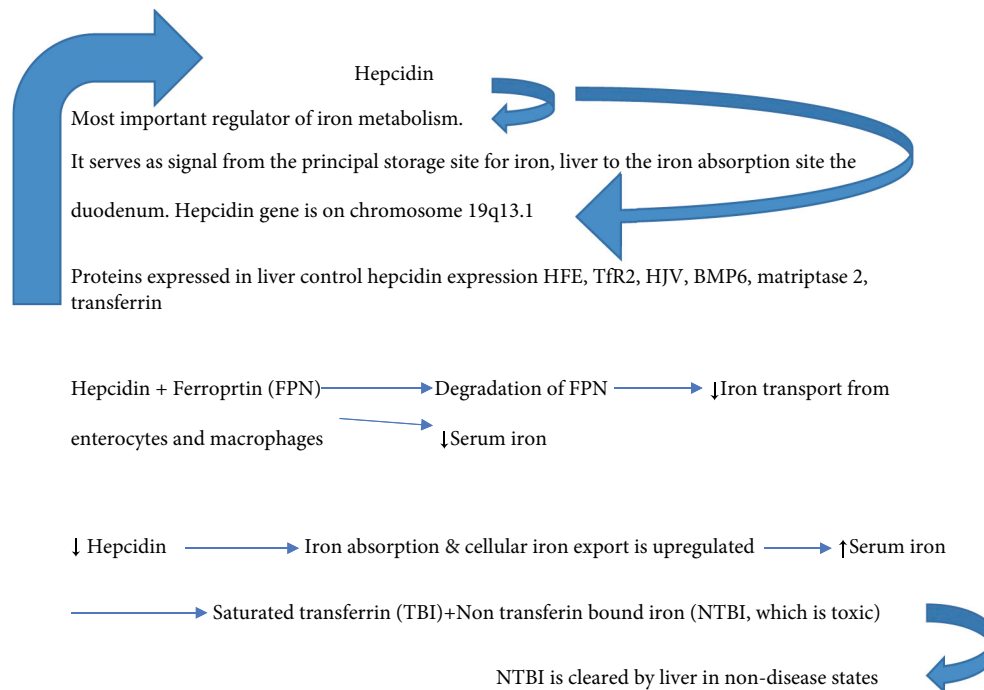


FIGURE 3: Flow chart for hepcidin as the main regulator of iron metabolism [3].

In C282Y homozygotes, the high serum ferritin level is $>200 \mu\text{g/l}$ in females and $>300 \mu\text{g/l}$ in males and postmenopausal women. Excess tissue iron >25 micro moles/g was seen in 52% of females and 75% of males after liver biopsy in 50% of all C282Y homozygotes. Approximately 10%-33% of C282Y homozygotes eventually develop haemochromatosis-associated mortality. In other studies, liver fibrosis and cirrhosis were present in 18% and 2% of females and 5% and 6% of males, respectively. Organ damage is observed when parenchymal iron storage is $>20\text{g}$. Cirrhosis is 13 times and cardiomyopathies are 30 times more likely in HFE HH [2, 5]. Diabetes mellitus is either due to a lack of insulin from B-cell damage in the pancreas or due to an increase in insulin resistance. The serum ferritin level is not predictive of diabetes mellitus development. Thyroid dysfunction can manifest as both hyperthyroidism and hypothyroidism. The second and third metacarpophalangeal joints are involved in 20% to 50% of patients; other joints include proximal interphalangeal joints, the wrist, elbow, shoulder, and hip. Arthropathy is generally symmetrical and polyarticular, and patients present with chronic pain, joint stiffness, bony enlargement, and minimal signs of inflammation. Approximately 25% of patients with HH have osteoporosis.

Approximately 90% of patients have hyperpigmentation due to melanin and iron deposition in basal layer of epidermis and around sweat glands which is more noticeable on sun-exposed area such as face, neck, and extensor surface of the lower forearms, dorsum of the hands, lower legs, and old scars. Skin is brownish bronze or slate grey, and the cutaneous atrophy, flattened nails, and loss of body hair can happen [3, 5].

3.1.5. Diagnosis. Normal serum ferritin levels of $<200 \mu\text{g/l}$ in premenopausal women and $<300 \mu\text{g/l}$ in men and postmenopausal women with transferrin saturation of $<45\%$ have a negative predictive value of 97% excluding the iron overload [3]. Transferrin saturation is the best initial phenotypic screening test. A fasting transferrin saturation $>45\%$ detects almost all affected homozygotes. Unsaturated iron binding capacity (UIBC) is an alternative to transferrin saturation that is cheaper and performs equally well. Serum ferritin can be high in inflammation, hepatocellular necrosis, alcohol liver disease, nonalcoholic steatohepatitis, chronic hepatitis C, rheumatoid arthritis, and neoplastic disease. In these conditions, transferrin saturation is usually normal. An increase in $1 \mu\text{g/l}$ of serum ferritin reflects an increase of 7 mg of body iron stores. If either serum transferrin saturation (STS) or serum ferritin (SF) is high, genetic testing for HFE haemochromatosis is done.

Liver biopsy is used for prognostic values in HH, and in secondary iron overload diseases, either biochemical staining of iron or hepatic iron concentrations to calculate the hepatic iron index are done. Iron is mainly deposited in parenchymal hepatocytes and none in Kupffer cells, whereas in secondary iron overload diseases, iron staining in Kupffer cells is prominent. Indications for liver biopsy include age 40 years, serum ferritin $>1000 \mu\text{g/l}$, abnormal liver enzymes, hepatomegaly, or a combination of those in HH homozygotes.

Individuals with clinical iron overload and uninformative genetic analysis as well as compound heterozygotes with hepatomegaly, abnormal transferrin saturation, serum ferritin $>1000 \mu\text{g/day}$, and age >45 should also have liver biopsy. MRI has sensitivity of 89% and specificity of 80% using a

threshold of L/M ratio of <0.88 (L/M: liver and muscle ratio) to assess liver iron burden. MRI can detect liver iron concentration down to a threshold of 1.8 mg iron/g dry tissue. Sensitivity is 85%-94% and specificity is 92%-100% with greater accuracy in detecting lower iron concentrations. It also identifies the heterogeneous distribution of iron in the pancreas and heart. It differentiates between parenchymal (hepatic, pancreatic, and cardiac signals) and mesenchymal (splenic signal) iron overload. It also detects small iron free neoplastic lesions. The SQUID (superconducting quantum interference device) susceptometer allows in vivo measurement of the amount of magnetization due to hepatic iron. The results are quantitatively equivalent to those of liver biopsy, but it is not widely available. Transient electrography is used for the determination of advanced fibrosis and cirrhosis.

The workup involves, once iron overload is suspected, STS and SF. If STS saturation is high, the genetic testing for HFE HH is done. The same protocol is followed for the patients referred from the liver clinic.

C282Y/H63D compound heterozygotes and H63D homozygotes presenting with increased serum ferritin and serum transferrin saturation should be investigated for other causes of hyperferritinaemia.

If iron stores are high with a negative C282Y, perform either a liver biopsy or an MRI to confirm iron overload; if confirmed, then other hepatic or haematological diagnosis should be ruled out. In such cases, tests for other genetic mutations should be done, i.e., HAMP, HJV, TFR2, and FPN.

If only serum ferritin is high in suspected HH cases, rule out alcohol liver disease, inflammation (history and CRP), cell necrosis (ALT, AST, and CK), tumours (ESR and CT), nonalcoholic fatty liver disease (NAFLD), or metabolic syndromes (BP, cholesterol, triglycerides, and serum glucose). If none of the above conditions are found or treated but still increased SF, check again for STS, and if it is high, perform genetic testing. If C282Y/C282Y or C282Y/H63D are confirmed, the diagnosis of HFE HH is confirmed. If the genetic test is negative for HFE mutations, check for other genes.

If there is increased ferritin but decreased transferrin saturation or normal STS, then assess liver iron by MRI or by liver biopsy. If it is increased, rule out other causes; if none are found, check for nonhaemochromatosis iron overload disease, i.e., ferroportin disease or aceruloplasminemia. If the iron levels in the liver are normal, rule out the common causes of elevated ferritin before testing for a L-ferritin gene mutation (hyperferritinaemia-cataract syndrome). If a patient has an unclear presentation, check the family history of iron overload before checking for rare genetic disorders by genetic screening.

Noninvasive markers for detecting cirrhosis in HH include serum type 4 collagen which is elevated; a level of >115 ng/ml is sensitive but less specific. Serum hyaluronic acid >46.5 ng/ml showed 100% sensitivity and specificity in detecting cirrhosis in HH [4, 5].

The fibro scan, a noninvasive investigation, measures fibrosis by measuring liver rigidity. One limitation is obesity. Among CT and MRI, MRI is more sensitive and specific for

the detection of abnormal hepatic iron. A male C282Y homozygote with baseline serum ferritin between 300 and $1000 \mu\text{g/l}$ has a 25% chance of progressing to SF $>1000 \mu\text{g/l}$ on average after 12 years, with the greatest risk of progression among men with a baseline STS $>95\%$. In women with serum ferritin levels between 200 and $1000 \mu\text{g/l}$, only 18% will progress to serum ferritin $>1000 \mu\text{g/l}$ in the same time period. Therefore in C282Y homozygotes, if serum ferritin is normal, check for serum ferritin every 5 years. If compound heterozygote for C282Y/H63D, as only 1% of these subjects develop clinical disease, again if SF is normal, monitor every 2 to 5 years. For C282Y heterozygote, H63D heterozygote, and homozygote, the carrier state is 1 in 8. It is not associated with disease, so no monitoring required unless there are symptoms and abnormal iron studies [6].

3.1.6. Differential Diagnosis. Differential diagnosis includes iron overload conditions due to other genes causing primary hereditary haemochromatosis and iron overload due to secondary causes. These include non-HFE haemochromatosis caused by HAMP, HJV, TFR-2, and FPN. In secondary causes, there is "iron overloading anemia such as thalassemia and sideroblastic anaemia"; "chronic hemolytic anaemia such as aplastic anaemia and pyruvate kinase deficiency"; "chronic liver disease that is hepatitis C infection, NAFLD, and alcoholic liver disease"; "porphyria cutanea tarda"; "iatrogenic such as red blood cell transfusion and long-term hemodialysis"; and "miscellaneous causes such as aceruloplasminemia, African iron overload, and neonatal iron overload."

Unlike primary HH, secondary iron overload conditions are associated with anaemia and iron accumulation is in macrophages. The patients are treated with chelation due to the associated anaemia and not phlebotomy. In thalassemia, iron overload occurs in the spleen unlike in HH patients. Serum ferritin concentrations in patients with aceruloplasminemia are similar to those in patients with haemochromatosis [3].

3.1.7. Treatment and Prevention. The five treatment and prevention modalities are phlebotomy, iron chelation, therapeutic erythrocytapheresis, hepcidin agonists, and liver transplantation.

With regard to phlebotomy, premenopausal women with SF $<200 \mu\text{g/l}$ and men and postmenopausal women with SF $<300 \mu\text{g/l}$ require no treatment. In mild to moderate conditions such as SF above 200-300 $\mu\text{g/l}$ but $<1000 \mu\text{g/l}$ and normal liver function tests, there is no clear advice. Watch and see or prophylactic blood donation is an option. Each phlebotomy removes 500 ml of blood amounting to 250 mg of iron in persons with a normal haematocrit. The amount of iron can be calculated by multiplying the number of phlebotomies with 0.25. If haemoglobin (Hb) is less than 11 g/dl, the frequency of phlebotomy needs to be decreased.

Before each venesection, the haematocrit is measured, and if it is <32 , the procedure is postponed. Serum ferritin is measured every 10-12 phlebotomies, and if it is $<25 \mu\text{g/l}$, it indicates an iron deficiency state and the procedure should be withheld. In classical HH, the removal of 8-25 units of

blood will achieve the target SF. The target SF level is $<50 \mu\text{g/l}$ with phlebotomy, but some authors recommend a target value within the normal SF level as that might be better tolerated by patients, results in less anaemia, and prevents an increase in intestinal iron uptake caused by a decrease in hepcidin due to intensive bloodletting. Iron removal causes improvements in fatigue, malaise, elevated transferases, insulin requirement in diabetes, exercise tolerance, and cardiac function in one-third of cardiac cases. Arthropathy is less responsive, and it can worsen because iron can remain in the synovium and cartilage after phlebotomy. Iron depletion therapy does not eliminate the 10-30% risk of hepatocellular carcinoma and cholangiocarcinoma in patients with cirrhosis. Screening of patients of cirrhosis involves six monthly serum alpha fetoprotein tests and hepatic ultrasound.

Arthralgia and arthritis will require radiological evaluation and anti-inflammatory medicine. A podiatric evaluation, insoles in shoes to relieve foot pain, and a knee or hip replacement may be required. DEXA scan should be performed to rule out osteoporosis. Hypogonadotropic hypogonadism will need gonadotrophins with or without testosterone therapy. Hepatic decompensation with ascites, spontaneous bacterial peritonitis, encephalopathy, variceal haemorrhage, and an early small tumour may need assessment for a liver transplant.

Therapeutic erythrocytapheresis removes iron as haemoglobin and is useful in cases of massive iron overload to achieve the required serum ferritin in a short period of time with the duration of treatment decreasing by 70%.

Patients in whom iron deficiency occurs for no obvious reason should be referred for occult blood loss.

Subcutaneous desferrioxamine 1–2 g in 100–200 ml of water or normal saline is infused for over 10–12 hours during sleep for iron chelation. Indications for chelation are when phlebotomy cannot be done which is with iron overload and anaemia, circulating failure like congestive cardiac failure and difficult venous access. Side effects of desferrioxamine include gastrointestinal symptoms, dizziness, visual and auditory impairment, muscle cramps, tachycardia, and thrombocytopenia.

An orthotopic liver transplant can be done, and if the liver is from an HFE normal person, iron accumulation does not happen, and SF and STS remain normal. It indicates that the defect responsible for HFE HH lies in the liver as HFE interacts with hepcidin in the liver and the C282Y mutation interferes with this interaction leading to a low hepcidin level and increased iron absorption. Intensive deironing is required before a liver transplant. One-year survival is 54% compared to 79% in non-HH liver disease. In the first year after transplant, the most common causes of death in HH patients are fungal infection and cardiac complications.

Overall survival is normal in those who begin treatment before diabetes and cirrhosis develop. Even in cirrhotic patients, 5-year survival rate is 72–92% and 10-year survival is 47 to 75%.

Regular blood donation is a preventive measure for asymptomatic individuals identified through family studies.

Doses of vitamin C should not exceed 500 mg/day as it accelerates iron mobilization precipitating sudden death from cardiac dysrhythmias. Alcohol should be avoided as it accelerates the development of cirrhosis and hepatocellular carcinoma. Avoid iron-containing foods and supplements. Patients with HFE HH should be immunised against hepatitis B [2–7].

Hepcidin agonists increase hepcidin expression but are still being evaluated in the research settings. As per physiological role of hepcidin, in iron overload disorders, hepcidin concentration is significantly decreased; therefore, elevating its concentration is an optimal strategy to ameliorate the disorder.

There are 4 types of hepcidin agonists.

Mini hepcidin has a longer half-life than natural peptides and seems to decrease the iron overload in mice. PR65 does its action in 2 weeks but has side effects due to a sulfhydryl group in position 7. Another one without sulfhydryl group has been devised but it is expensive.

Small chain compounds include genistein and progesterone which cause hepcidin induction. Genistein is an isoflavone compound isolated from plants. Epitiostanol, progesterone, and mifepristone degrade ferroportin action. Another compound called as ferristatin 11 induces the internalisation and degradation of TfR-1 and inhibits iron uptake and serum iron levels. Icaritin and its analogues can cause hepcidin induction.

TMPRSS6 antagonists inhibit matriptase-2 and induce hepcidin. These include antisense nucleotides (ASO) which decrease sera and liver iron. Another RNA-based molecule called LNP-RNAi shows HAMP expression after 24 hours in a mouse. LNP-RNAi combined with deferiprone shows better results. Another matriptase-2 inhibitor called the Kunitz-type inhibitor hepatocyte growth factor activator inhibitor (HAI-1 and HAI-2) has shown better results in inhibiting matriptase-2.

BMP-6 (bone morphogenetic protein signalling) enhances hepcidin induction but can cause serious calcification. Further research into this class of medications may lead to therapies that will target the cause of the disease rather than its symptoms [8].

Finally, these patients with haemochromatosis should not be discriminated against, genetic tests should only be conducted with the patient's consent, and the results of these test should only be passed on to the patient as a matter of confidentiality. Patients though should be advised to inform their family members and advise them to see their GP. Many countries allow blood taken by phlebotomy from HH patients to be used as blood donation.

Patient organization: <http://european.haemochromatosis.eu/index2.html>

3.2. Section 2 Pregnancy and Haemochromatosis. A normal full-term pregnancy removes 1 g of iron from the mother. For women who are already on maintenance of treatment, their pregnancies usually do well. In such cases, iron supplements should be avoided and serum ferritin can be checked; if there is an increase, phlebotomy should ideally be delayed until the end of pregnancy unless hepatic and cardiac

complications are present. In cases of complications, patients should be cared for by multidisciplinary team.

There have been reports on pregnant women developing serious maternal complications of hereditary haemochromatosis such as severe diabetes insipidus, a rare condition. The patient needed resuscitation at admission and treatment with desmopressin tablets during pregnancy. Treatment for haemochromatosis was initiated after pregnancy with desferrioxamine [9]. A 35-year-old parturient developed systolic heart failure with a 15% left ventricular ejection fraction, severe pulmonary hypertension, mitral insufficiency, cirrhosis, obstructive sleep apnoea, gestational diabetes mellitus, and severe sclerosis and was admitted to a medical intensive care unit at 32 weeks of pregnancy. She was stabilised and then induced at 34 weeks. She had a successful normal delivery [10]. Another 26-year-old woman who needed gonadotrophins because of hypogonadotropic hypogonadism of unknown origin to conceive was admitted with congestive cardiac failure. Investigations did not confirm a genetic mutation for HFE haemochromatosis, but iron parameters were high. In history, she had a sister who had hypogonadotropic hypogonadism and abnormal iron parameters. She was clinically diagnosed with juvenile haemochromatosis and managed accordingly [11]. One can see that if not treated, HH can cause severe cardiovascular complications in pregnancy.

In their study, You-Lin Tain et al. discovered that in mothers with thalassemia or haemochromatosis, their odd ratio of having a baby affected with congenital anomalies of the kidney and urinary tract was 5.69 [12].

In haemochromatosis, along with elevated iron absorption, there is increased absorption of chemically related heavy metals like lead. Lead can be taken from food, contaminated air, and dust. It accumulates in bones and has a half-life of 30 years. It has adverse effects on mainly renal, neurologic, and haematopoietic systems.

Lead has been linked to hypertension in adults since the 1980s. Kennedy et al. examined 9 studies in a review and found a significant association in six of them between maternal blood lead concentration and gestational hypertension and preeclampsia below 10 µg/dl. Lead increases reactive oxygen species (ROS) increasing oxidative stress and causing endothelial dysfunction [13]. Jameil found in her study that mean serum levels of lead in maternal blood were higher in women with gestational hypertension and preeclampsia than in the control group.

The increase was significant ($P < 0.05$) only for the preeclamptic group when it was compared with the control group. The cutoff used in this study was 10 µg/dl [14]. Maternal lead levels are quite high in Jameil's study, but the CDC only recommends chelation if the level is at or above 45 µg/dl in pregnancy [15].

The neurodevelopment begins in the intrauterine foetal period when the blood-brain barrier is still immature. Therefore, the foetus is most susceptible. Foetal exposure to lead begins at 21 weeks and continues throughout the foetal period. The placenta cannot protect the foetus from the lead exposure in the mother's blood. The transfer of lead can be modified by maternal iron deficiency or iron uptake.

Genes related to iron metabolism can modify lead absorption, leaving pregnant women with haemochromatosis at an increased risk of foetal lead exposure. Lead exposure in utero can cause lead deposition in the foetal brain causing neurodevelopmental and cognitive abnormalities [13].

Karwowski et al. discovered a nonsignificant association of maternal HFE C282Y gene variant status and placental lead transfer [16]. In Kayaalti et al.'s study, it was found that maternal iron levels were higher in mothers with H63D, genotype of HD+DD (heterozygote+homozygote atypical) compared to genotype HH (homozygote typical for H63D). The maternal placental and umbilical cord blood levels of lead in mothers with the HD+DD genotype were higher than the HH genotype. A 1% increase in maternal lead was predicted to increase placental lead by 0.74% and umbilical cord lead by 0.49% in infants born to mothers with the HD+DD genotype compared to the HH genotype where the above change in maternal lead increases placental lead by 0.20% and umbilical cord lead by 0.04%. Therefore, in regression analysis, at maternal lead levels of 5 µg/dl, placental lead will be 3.7 µg/dl and the umbilical cord lead level will be 2.45 µg/dl in infants whose mothers had the HFE H63D variant. This relationship was unaffected by maternal blood iron level, foetal gestational age, foetal birth weight, length, head circumference, socioeconomic status, or placental weight. Hence, genetically susceptible mothers with haemochromatosis mutations cannot be protected even if environmental and occupational lead exposure is limited. The underlying mechanism is an increase in DMT-1 in the duodenum and placenta which, along with increased iron absorption, has an increased affinity for lead absorption and results in significant lead transfer to the foetus in mothers who have genotype HD+DD. The women in this study were not exposed to lead in the environment [17].

Maternal haemochromatosis increases lead absorption and transfer to the foetuses which in turn can increase the risk of congenital abnormalities. Foetal lead exposure seems to have caused the reduced birth weight and birth size, neurodevelopmental disorders, and subclinical brain damage [18, 19]. According to the ALSPAC study, when blood lead levels were <5 µg/dl, there was significantly linear negative association with birth weight, head circumference, and crown heel length. Lead induced free oxygen radicals that can cause collagen damage in amniotic membrane leading to preterm rupture and delivery. As a result, population with high lead exposure and a high prevalence of iron overload conditions such as haemochromatosis are expected to have an increased risk of adverse prenatal outcomes [20]. Hong et al. also reported prenatal exposure of <5 µg/dl and adverse effects of lead on postnatal growth.

These findings support the notion that the high levels of lead can cause foetal adverse outcomes in susceptible mothers, in haemochromatosis [21]. Schnaas et al. found that lead exposure at 28 weeks of gestation which is the crucial period for intellectual development is neurotoxic and can cause irreparable damage to foetal brain. Lead can enter breast milk as a result of calcium mobilization from bones due to the increased demand for calcium caused by breastfeeding increasing the neonate's exposure to lead [22].

In summary, mothers with haemochromatosis may have high lead levels as a result of increased iron absorption and mobilization of previously stored high levels of lead in the bones with calcium as a result of increased calcium demand. The mothers also have a genetic component that increases lead absorption regardless of whether the patient is exposed to an increased lead environment or not. Lead is associated with maternal gestational hypertension and preeclampsia and can cause congenital abnormalities in the foetus and growth problems in both the foetus and newborn.

In another study, Sammallahti et al. examined that maternal serum ferritin levels during pregnancy are associated with child's cognitive abilities. They looked at the data on maternal ferritin and at one child's neurodevelopmental outcome in 2479 mother and child pairs. 387 mothers had low iron ferritin (mean 20.6 $\mu\text{g/l}$), 1700 had intermediate iron ferritin (mean 64.6 $\mu\text{g/l}$), and 392 had high iron ferritin (mean 170.3 $\mu\text{g/l}$) in early pregnancy. Children underwent tests for cognitive abilities at the age of 4-9 years. High maternal ferritin was associated with 2.54 points lower child intelligent quotient and 16.02 cm^3 smaller brain volume. Low maternal iron ferritin was not associated with child's cognitive disabilities. Maternal ferritin was unrelated to child's motor outcome. They thus concluded that maternal iron status during pregnancy may be associated with offspring's neurodevelopment [28].

In patients suffering from sickle cell disease, the incidence of pulmonary arterial hypertension is 4-6% in adults which is 1000 to 3000 times higher than the general population. Patients with sickle cell disease have high levels of PIGF (insulin-like growth factor), a member of vascular endothelial growth factor family and endothelin 1 (ET1, a potent vasoconstrictor). They cause pulmonary vasoconstriction, right ventricular hypertrophy, and histological evidence of pulmonary hypertension. PIGF can also cause in adults high tricuspid peak velocity of regurgitation, an echocardiographic marker of risk for high pulmonary artery pressure. This high tricuspid regurgitation peak velocity is correlated with high ferritin and transferrin which in turn increases the PIGF value. Wong et al. found in their study that patients with iron overload disorders like SCD and haemochromatosis have high level of PIGF due to hemin stimulation of primary erythroid progenitor cells expressing erythroid developmental transcription factor (EKLF) which in turn causes the release of PIGF. ET1 is the final common pathway. They discovered that haemochromatosis patients have features of endothelial dysfunction but not pulmonary hypertension [23]. However, based on the case reports mentioned earlier in this review and the additional studies that will be included in this review, it is clear that haemochromatosis can cause severe cardiovascular problems including pulmonary hypertension. The likely difference is that sickle cell disease is a more severe iron overload disorder with an earlier and more acute onset of complications if not treated, whereas haemochromatosis is late onset and chronic and late onset are complications. Hannes Gaenger et al. also supported the concept that in haemochromatosis patients, there is impaired endothelial dysfunction which is mainly reflected in male and untreated patients. Females have rela-

tive protection due to menstruation. The high level of iron (increased SF and increased STS), increased TBARS (thio-barbituric acid reactive substance), and decreased radical scavenger, glutathione, result in oxidative stress which impaired endothelium-dependent dilatation of brachial artery (EDD) and increased intima media thickness (IMT) of the carotid artery.

Both increased IMT and decreased EDD are reliable markers of early structural vascular pathology associated with cardiovascular risk and coronary heart disease prevalence. After decreasing iron levels, EDD returns to normal level but IMT remains the same, though further increases in IMT can be prevented [24].

Dorak et al. tested the concept that genetic variants in the haemochromatosis increase iron overload and can also increase birth weight and the risk of leukaemia in children by increasing cell proliferation rate and through the genotoxic effects of iron excess. A total of 1117 infants were selected from the mother-infant pairs as control group in the North of England. DNA samples were collected from 163 children aged <16 with childhood acute lymphocytic leukaemia. Birth weight was noted to increase with foetal HFE variants of C282Y and H63D as well as compound heterozygotes by 91.1 g, 62.5 g, and 282.2 g, respectively, in male infants. In female foetuses, the birth weight was higher but less than in males if they had the above genotypic mutations. Another HFE variant IVS1 increased birth weight in both sexes by 129.9 g. If a foetus was affected with any of the above HFE variants and had TfRC heterozygosity or homozygosity, the increase in birth weight was 281 g and 538 g, respectively, in male babies. In females, the change was minimal and not significant. The combined influence of HFE and TfRC genotype on infant birth weight was further augmented by maternal HFE mutations positively, from 168 g to 235.7 g, respectively. It was found that if infant had HFE IVS1 variant+TfRC and maternal HFE variant, then increase in weight was by 714 g. Two of the three males in this group weighed >4500 g. None of the HAMP variants showed any significant association with birth weight in either sex. The cord blood iron level was lower in male infants compared to female infants, and it was speculated that male babies were using iron to increase weight and hence had less cord blood iron than female babies and vice versa. Male infants who had HFE variants themselves along with the HFE gene mutation in their mothers had higher birth weights and higher foetal cord iron levels showing the double effect. The greater the association of HFE variants with birth weight, the smaller the magnitude of the association with leukaemia as the risk was shown to be higher in females and higher only in males with higher birth weight and higher serum cord iron as previously mentioned [25].

In a Norwegian mother and child cohort study, Stordal et al. investigated 94209 pregnancies and showed that incidence of type 1 DM was higher in the children whose mother had iron supplementation than the ones whose mothers did not have iron supplementation. A total of 373 children had type 1 DM. Adjusted hazard ratio was 1.33. They also said that maternal HFE genotype causing high and intermediate iron stores was associated with offspring's

diabetes. The odd ratio for this was 1.45 with confidence interval of 1.04-2.02 [29].

Therefore, in summary, certain maternal and foetal HFE/TfRC combinations increase foetal iron overload which results in higher birth weight in both sexes but significantly in males. Iron use directed towards foetal growth prevents its toxic effects to cause leukaemia. Therefore, females are at higher risk of childhood leukaemia, and male foetuses have high risk of leukaemia if they have higher birth weight and higher cord iron levels as a result of double effect mentioned earlier.

Hence, mothers who have been diagnosed with haemochromatosis need to be monitored for SF and STS, and if they are high, treatment which is phlebotomy is postponed until delivery, unless complications arise. These mothers also need to be monitored for the risk of gestational hypertension and preeclampsia, CVS disease, pulmonary hypertension, and DM. Foetal monitoring not only involves a careful anomaly scan but also serial growth scans to rule out both IUGR and LGA. As a part of genetic counselling, mothers should be counselled about the possible link between childhood leukaemia and type 1 DM and their genes especially if the father is a heterozygote or homozygote. These mothers will need to see a pediatrician to determine what will be involved in their babies' follow-up to rule out any neurodevelopmental delays and cognitive abnormalities.

I want to raise a question at the end of this discussion, as we discovered that rare types of HH cause severe iron overload and LGA babies [25]. According to Wong et al. [23], severe iron load induces high levels of PIGF from nonplacental sources. Could this high PIGF be responsible for increased birth weight in certain HH mutations? Low PIGF levels are associated with small for gestational age and IUDs because of absent trophoblastic invasion of the spiral arteries which is required for adequate blood supply and nutrients to developing baby [26, 27]. Further research is required in this area.

4. Conclusion

Primary iron overload disorders of which HFE haemochromatosis is the most common can cause multiorgan maternal complications, i.e., cardiovascular problems, pulmonary HTN, DM, and preeclampsia. It can also increase the risk of congenital abnormalities and growth problems in the foetus. One mechanism is through an associated increase in lead absorption or mobilisation from the bones. Another is that high levels of PIGF of erythroid cells origin in haemochromatosis can cause endothelial dysfunction in the mother increasing cardiovascular complications. Infants with haemochromatosis mutations are at higher risk of developing childhood leukaemia and are large for gestational age which may increase further if their mothers also have the mutation. More research is required in these areas.

As a result, pregnant mothers with haemochromatosis despite normal or mildly raised iron parameters need monitoring for an increased risk of gestational hypertension and preeclampsia, CVS problems, pulmonary hypertension, and DM. Foetal monitoring should include anomaly scan and growth scans in anticipation of both IUGR and

LGA. Patients should be counselled about the increase in the risk of childhood leukaemia and neurodevelopmental delays for which their babies will require long-term follow-up with a pediatrician. Agents like hepcidin agonists are being evaluated and hopefully the near future will bring medications that will ameliorate the disease by acting on its pathophysiology.

Abbreviations

HFE:	High ferrous
HH:	Hereditary haemochromatosis
HAMP:	Hepcidin gene
HJV:	Hemojuvelin
FtR2:	Ferritin transport receptor 2 gene
FPN:	Ferroportin gene
Fe ³⁺ :	Ferric
Fe ²⁺ :	Ferrous
DMT:	Divalent metal transporter 1
TBI:	Transferrin bound iron
TfR-1:	Transferrin receptor 1
IRE:	Iron responsive element
IRP-1:	IRE binding protein 1
IRP-2:	IRE binding protein 2
BMP6:	Bone macrophage protein 6
NTBI:	Nontransferrin bound iron
RR:	Relative risk
ECG:	Electrocardiogram
UIBC:	Unsaturated iron binding capacity
STS:	Serum transferrin saturation
SF:	Serum ferritin
MRI:	Magnetic resonance imaging
L/M ratio:	Liver and muscle ratio
SQUID:	Superconducting quantum interference device
CRP:	C-reactive protein
ALT:	Alanine transferase
AST:	Aspartate transferase
CK:	Creatine kinase
ESR:	Erythrocyte sedimentation rate
CT:	Computerized tomography
NAFLD:	Nonalcoholic fatty liver disease
BP:	Blood pressure
Hb:	Haemoglobin
DEXA:	Dual energy X-ray absorptiometry
ASO:	Antisense nucleotide
HAI-1:	Hepatocyte growth factor activator inhibitor 1
HAI-2:	Hepatocyte growth factor activator inhibitor 2
GP:	General practitioner
ROS:	Reactive oxygen species
Na/K:	Sodium potassium
ATP:	Adenosine triphosphate
Ca:	Calcium
IGF-2:	Insulin-like growth factor 2
PIGF:	Placental insulin-like growth factor
SCD:	Sickle cell disease
EKLF:	Erythroid developmental transcription factor
ETI:	Endothelin inhibitor
TBARS:	Thiobarbituric acid reactive substance
EDD:	Endothelium-dependent dilatation of brachial artery

IMT:	Increased intima media thickness
IUD:	Intrauterine death
IGF-1:	Insulin-like growth factor 1
IGFBP-1:	Insulin-like growth factor binding protein 1
IGFBP-2:	Insulin-like growth factor binding protein 2
IGFBP-3:	Insulin-like growth factor binding protein 3
IUGR:	Intrauterine growth retardation
LGA:	Large for gestational age.

Data Availability

It is in the form of tables in the supplementary files. Figure 1 presents the flow chart for the search criteria, which describes how the search was carried out. References are given in the main manuscript file.

Additional Points

Strengths. We have included many review articles about haemochromatosis in general, covering the time period from 2002 to 2022. (i) Newer data linking iron metabolism and heavy metals such as lead as well as biomarkers such as placental insulin-like growth factor and their association with foetal complications has been gathered and has not previously been included in any review. (ii) Case reports indicating very serious maternal complications like pulmonary hypertension and cardiac failure in pregnancy due to haemochromatosis were included in this article. (iii) This review has examined the effects of pregnancy on haemochromatosis and the effects of haemochromatosis on pregnancy in depth, which has not been done in any of the reviews before. **Limitations.** Data is retrospective: (i) English language and (ii) only human.

Consent

Informed consent was obtained from all participants.

Conflicts of Interest

The author declares that they have no conflicts of interest.

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Supplementary Materials

It includes the following tables: PRISMA checklist, characteristics of reviews, characteristics of observational studies, and characteristics of case reports. (*Supplementary Materials*)

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