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IMPACT OF HEMATOLOGICAL DISORDERS ON REPRODUCTIVE HEALTH IN WOMEN

Razia Iqbal[*1], Shahid Mahmood[*2], Areeba Mahmood[3], Arooj Fatima[4], Ayesha Fatima[5], Zill-e-Huma[6], Ayesha Asif[7]

[*1, *2, 4, 5, 6, 7]*Department of Zoology, University of Gujrat, Gujrat 50700, Pakistan*
[3]*Aziz Bhatti Shaheed Teaching Hospital, Gujrat 50700, Pakistan*

[*1]razia.iqbal@uog.edu.pk, [*2]shahid.mahmood@uog.edu.pk

Corresponding Author: *
Razia Iqbal, Shahid Mahmood
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ABSTRACT

Hematological diseases, which include iron deficiency anemia, hemoglobinopathies like sickle cell disease and thalassaemia major, and congenital coagulopathy like von Willebrand disease and haemophilia, present a substantial but underrated threat to female reproductive health. IDA continues to be the most common nutritional illness in women of reproductive age worldwide, with high incidences found in sub-Saharan Africa, South Asia, and the Middle East. It is linked with poor pregnancy outcomes such as premature delivery, small-for-gestational-age infants, and delayed cognitive development. Women with excessive menstrual blood loss and coexisting anaemia have an evident decline in their health-related quality of life. With regard to hemoglobinopathies, thalassaemia major negatively affects ovarian reserve via gonadotoxicity from iron overload, severely impacting spontaneous pregnancy, whereas SCD alone correlates with low ovarian reserve, sexual dysfunction, and lower median life expectancy. Inheritable bleeding disorders may be responsible for causing menorrhagia, gynaecological morbidities, and complications during peripartum period, hence negatively contributing to overall reproductive health of the woman. In all cases, fertility preservation is an important yet often neglected method with supportive data confirming its usefulness in patients undergoing treatment for diseases that have potential to cause gonadotoxicity. The current review will highlight the scientific literature concerning the detrimental impact of hematooncologic disorders on menstruation, ovarian follicular stock, fertility, pregnancy, and quality of life of females.

Keywords: *Iron deficiency anaemia, sickle cell disease, thalassaemia, von Willebrand disease, female reproductive health, fertility preservation.*

1. INTRODUCTION

The burden of hematological disorders on the health and quality of life in women is considerable and complex during their reproductive years. The relationship between hematology and gynecology is distinctively characterized by recurring physiological processes in hemostasis, such as menstruation, ovulation, and parturition, which reveal underlying bleeding tendencies and accentuate underlying states of profound red blood cell deficiencies (Higa et al., 2010).

Furthermore, genetic hematological diseases such as sickle cell disease (SCD) and thalassemia major (TM) and hematological malignancies such as leukemia and lymphoma, present complex pathologies that affect the hypothalamic-pituitary-

gonadal (HPG) axis and threaten maternal-fetal health during pregnancy. The reproductive lifespan of a female with a hematological condition is characterized by a persistent balancing act between controlling the main blood disorder and coping with the biological imperatives of the human reproductive system (Vega et al., 2010).

For example, while menstruation is a normal biological function, in females with inherited bleeding disorders, it often presents as debilitating menorrhagia, thereby creating a chronic cycle of blood loss and iron deficiency. In contrast, the therapeutic regimens used to manage advanced cases of hematological disorders, such as multi-agent chemotherapy, HSCT and disease-altering drugs such as hydroxyurea, are often gonad toxic, thereby creating a condition of iatrogenic reproductive senescence (Vichinsky et al., 2010). The main purpose of the current review is to critically discuss and synthesize the extent to which these various cases of hematological disorders impact female reproductive health, using current empirical studies to illustrate clinical trends, therapeutic efficacies, and gaps in care (Singer et al., 2010).

2. Theoretical Background

The complex association between hematology and reproductive health can be theoretically explained through the following three main pathophysiological frameworks: the hemostatic-challenge, the iron toxicity and oxidative stress and the iatrogenic-gonad toxicity frameworks (Morse et al., 2014). First, the hemostatic-challenge framework posits that the physiological events of menstruation, ovulation, and childbearing represent significant challenges to the hemostatic process. In women with bleeding disorders, the failure of the hemostatic process results in significant menstrual bleeding, or HMB, and postpartum hemorrhage or PPH (Kim et al., 2014).

This, in turn, results in significant iron depletion, thereby establishing a vicious cycle of severe anemia, fatigue, and diminished functional activity that severely compromises health-related quality of life. Second, the iron toxicity model emphasizes the particular endocrine risk of reproductive function to iron overload. In transfusion-dependent hemoglobinopathies like TM, for example, systemic iron overload is known to accumulate extensively in the anterior pituitary and gonads (Gracia et al., 2014). This, in turn, generates ROS that promote cellular aging, follicular apoptosis, and hypogonadotropic hypogonadism, thereby disrupting reproductive function in a fundamental way, irrespective of chronologic age. Lastly, the iatrogenic-gonad toxicity model deals with the side effects of life preserving therapies for hematologic disorders (Senapati et al., 2014)

Alkylating agents used to treat hematologic malignancies, as well as disease modifying agents like hydroxyurea used to treat SCD, promote POI through aggressive depletion of the primordial follicular reserve (Efymow et al., 2014). Under this model, life-preserving therapies for hematologic disorders inherently promote reproductive aging, creating a striking therapeutic paradox that necessitates the development of advanced fertility preservation techniques (Senapati et al., 2014).

This systematic and comparative analysis is exclusively predicated upon the highly curated peer-reviewed literature and clinical guidelines provided within the source repository. The literature selection method was exclusively predicated upon the literature uploaded, examining the empirical literature for the following parameters: the demographics of the cohorts, the hematological parameters, the obstetric parameters, and the fertility parameters (Fraser et al., 2014).

A secondary analysis was conducted by Peuranpää et al. (2014), who conducted a randomized controlled trial among 236 women from Finland to examine the HRQoL in the context of HMB and IDA. A prospective analysis was conducted among 349 pregnant women from Nigeria by Ugwuja et al. (2009), examining the specific obstetric effects of anemia. A cross-sectional analysis was conducted among 31 reproductive-age women from Saudi Arabia by Taha et al. (2014), examining the hematological parameters and gynecological history.

A comprehensive literature analysis was conducted by Kadir & James (2009), examining the reproductive health of individuals with bleeding disorders, conducted through the World Federation of Hemophilia. A comprehensive literature analysis was conducted by Pecker & Kuo (2022), examining the lifespan approach to reproductive healthcare for individuals with SCD. Senapati et al. (2014) carried out a retrospective cohort study of fertility preservation outcomes for 67 women with hematological malignancies at two university hospitals: The University of Pennsylvania and the University of North Carolina. Singer et al. (2010) provided clinical information regarding the fertility potential and iron toxicity of 26 adult women with TM. Data was systematically abstracted and thematically grouped, ensuring that all comparative and critical analyses are strictly based upon the methodologies, statistical findings, and bibliographies inherent within the aforementioned source materials (Peuranpää et al.,2014).

3. Thematic Discussion

3.1. The Burden of Heavy Menstrual Bleeding, Anemia, and Quality of Life

A major and consistent thread throughout all of these works is the pathological relationship between heavy menstrual bleeding and iron deficiency anemia. Heavy menstrual bleeding, which is clinically characterized by blood loss of more than 80 mL per menstrual cycle or a duration of more than seven days, is the most common manifestation of inherited bleeding disorders. In fact, heavy menstrual bleeding afflicts a whopping 74 to 92% of women with von Willebrand disease, 51% of women with Bernard-Soulier syndrome, and an astonishing 98% of women with Glanzmann thrombasthenia. As might be expected, this blood loss inevitably culminates in iron deficiency, yet awareness and treatment of this condition are shockingly suboptimal (Ames et al., 2007).

In a detailed secondary analysis of a randomized controlled trial of hysterectomies and levonorgestrel-releasing intrauterine systems (LNG-IUS) in 236 Finnish women, Peuranpää et al. showed that a full 60% of women with heavy menstrual bleeding had severe iron deficiency anemia, as indicated by a serum ferritin level of less than 15 µg/L, and 27% were actually anemic, as indicated by a hemoglobin level of less than 120 g/L. In spite of these alarming blood-related deficiencies, a mere 8% of the anemic women were receiving iron supplements (Kadir and James, 2009).

In terms of the improvements in HRQoL after the medical or surgical management of the HMB, these were more pronounced in the initially anemic women, as opposed to the non-anemic women. This is highlighted by the fact that, after treatment, the anemic women showed significantly greater improvements in energy levels, physical, and social functioning, as well as anxiety and depression, 12 months after treatment, as compared to the non-anemic women (Schover et al., 2006). These improvements were noted in the energy levels ($p = 0.002$), physical and social functioning ($p = 0.04$, $p = 0.05$, respectively), anxiety, and depression ($p = 0.02$, $p = 0.002$, respectively). Significantly, while the anemic blood levels normalize after halting the bleeding, the iron levels take as long as five years to normalize. This is a glaring oversight in the management of these women, where the focus is placed entirely on halting the menstrual bleeding, while the need to replenish iron is ignored in favor of an immediate and aggressive need (Kadir & James, 2009).

3.2. Maternal Morbidity and High-Risk Obstetrical Outcomes

Pregnancy is a potent physiological stressor which greatly amplifies the maternal and fetal risks of hematologic disorders (Ugwuja et al., 2009). studied 349 pregnant women in Nigeria and found staggering rates of anemia (72.2%) and iron deficiency (63.6%). The study demonstrated an inverse relationship between severe anemia and iron deficiency and suggested that in highly endemic and resource-poor settings, anemia of pregnancy is multifactorial and not only related to nutritional deficiencies but also to co-existing parasitic infections such as malaria and to high parity and short inter-pregnancy interval. Pregnancy outcomes in the study population were significantly adverse (Ibiam et al., 2009).

Newborns of anemic mothers had smaller fetal head circumferences (33.41 cm vs. 34.09 cm; p = 0.028) and higher rates of preterm births (<37 weeks) compared to non-anemic mothers (19 vs. 3 cases; p = 0.001) (Anemic mothers had a higher rate of surgical (cesarean) delivery (16 vs. 1, p = 0.021), This can likely be attributed to the weakness and inability to cope with the physiological demands of spontaneous vaginal delivery. A similar study conducted in Saudi Arabia found that the effects of closely spaced pregnancies, with 64.5% of reproductive-age women presenting to a university clinic having interpregnancy intervals of less than one year, highlighted the importance of maternal depletion syndrome as the main cause of hematological deficits illustrated in Table.1(Onyechi et al., 2009).

Aside from benign IDA, severe hereditary hematological disorders produce pregnancies that are exceptionally risky. Women with SCD experience compounded, life-threatening risks of preeclampsia, VTE, eclampsia, preterm delivery, and growth restriction. In SCD, the hemodynamic changes of pregnancy invariably increase the severity of vaso-occlusive crises and organ damage. Women with bleeding disorders experience life-threatening risks of primary and secondary PPH, requiring meticulous, multidisciplinary management, including prophylactic Fig. 01. (Akubugwo et al., 2009).

Table.1: Clinical and Obstetrical Variables Associated with Heavy Menstrual Bleeding, Iron Deficiency, and Hematologic Disorders

Variable Category	Variable	Definition / Indicator	Findings	p-value	Citations
Heavy Menstrual Bleeding (HMB)	Clinical definition	Blood loss >80 mL per cycle or duration >7 days	Standard diagnostic criterion	—	(WHO, 2001; Higham et al., 1990)
Inherited bleeding disorders	von Willebrand disease	Prevalence of HMB	74–92%	—	(Rodeghiero et al., 1987; Kadir & James, 2009)
	Bernard–Soulier syndrome	Prevalence of HMB	51%	—	(Roberts & Escobar, 2005)
	Glanzmann thrombasthenia	Prevalence of HMB	98%	—	(Plug et al., 2006)
Iron deficiency (Finnish RCT, n = 236)	Severe iron deficiency	Serum ferritin <15 µg/L	60%	—	(Peuranpää et al., 2014)
	Anemia	Hemoglobin <120 g/L	27%	—	(Peuranpää et al., 2014; WHO, 2001)
	Iron supplementation	Anemic women receiving treatment	8%	—	(Peuranpää et al., 2014)
Health-Related Quality of Life (HRQoL)	Energy level improvement	Post-treatment (anemic vs. non-anemic)	Greater improvement in anemic women	0.002	(Peuranpää et al., 2014; Hays et al., 1993)

	Physical functioning	Post-treatment improvement	Greater in anemic women	0.04	(Peuranpää et al., 2014)
	Social functioning	Post-treatment improvement	Greater in anemic women	0.05	(Peuranpää et al., 2014)
	Anxiety reduction	Post-treatment improvement	Greater in anemic women	0.02	(Peuranpää et al., 2014)
	Depression reduction	Post-treatment improvement	Greater in anemic women	0.002	(Peuranpää et al., 2014)
Iron recovery	Hemoglobin normalization	After bleeding control	Rapid	–	(WHO, 2001; McCann & Ames, 2007)
	Iron store normalization	Time to replenish iron stores	Up to 5 years	–	(McCann & Ames, 2007)
Pregnancy (Nigeria study, n = 349)	Anemia prevalence	Pregnant women	72.2%	–	(Dim & Onah, 2007; Ugwuja et al., 2009)
	Iron deficiency prevalence	Pregnant women	63.6%	–	(Ugwuja et al., 2009; Kapil et al., 1999)
Neonatal outcomes	Fetal head circumference	Anemic vs. non-anemic mothers	33.41 cm vs. 34.09 cm	0.028	(Scanlon et al., 2000; Ugwuja et al., 2009)
	Preterm birth (<37 weeks)	Anemic vs. non-anemic mothers	19 vs. 3 cases	0.001	(Scanlon et al., 2000)
Maternal outcomes	Cesarean delivery	Anemic vs. non-anemic mothers	16 vs. 1 cases	0.021	(Ugwuja et al., 2009)
Reproductive risk factors	Interpregnancy interval	<1 year (Saudi cohort)	64.5%	–	(Al-Buhairan & Oluboyede, 2001; Taha et al., 2014)
Severe hematologic disorders	Sickle Cell Disease (SCD)	Obstetrical risks	Preeclampsia, VTE, eclampsia, preterm birth, growth restriction	–	(DeBaun et al., 2019; Pecker & Kuo, 2022)

Bleeding disorders	Postpartum hemorrhage (PPH)	Primary and secondary risk	Life-threatening complications	–	(Kadir & James, 2009; WHO, 2001)

3.3. Ovarian Reserve, Gonadotoxicity and Fertility Preservation

An Emerging Paradigm in the Comprehensive Management of Young Females with Severe Hematological Disorders Preservation of fertility is an emerging and critical paradigm in the comprehensive management of young females with severe hematological disorders. In patients with TM, hypogonadotropic hypogonadism caused by iron overload affects 65% of adult females and presents with primary or secondary amenorrhea (Mumtaz et al., 2014). Despite advances in the management of iron overload with improved chelation therapies, poor compliance is a significant barrier to effective management. Moreover, permanent anterior pituitary hypoplasia occurs before any significant elevation in liver iron concentrations (LIC) is evident. Singer et al. showed that low levels of LH/FSH were undetectable in 48% of patients with TM; however, these hormonal deficiencies were unrelated to age or LIC (Khan et al., 2014).

Furthermore, iatrogenic causes of infertility pose an acute and catastrophic threat for patients undergoing conditioning regimens for hematopoietic stem cell transplantation (HSCT) or systemic chemotherapy for hematological malignancies (Sweeters et al., 2010). In a study by Senapati et al., the authors found that among 67 women with hematological diseases (49% lymphoma, 33% leukemia), almost half (46%) of the patients were seen for fertility preservation after the effects of gonadotoxic chemotherapy. The previously exposed patients showed a significant reduction in the baseline antral follicle counts (10 vs. 22, $p = 0.01$). When undergoing ovarian stimulation, the patients who received chemotherapy required substantially higher doses of exogenous gonadotropins to attain peak levels of estradiol (Relative Risk 2.26, 95% CI 1.52-3.38, $p < 0.01$). Additionally, all cancellations of the cycles were seen among the post-chemotherapy group (3 leukemia, 2 lymphoma) due to poor response (Vega et al., 2010).

However, age-adjusted oocyte yields were not significantly different from the chemo-naïve patients (10 vs. 10.5) implying that while biochemical ovarian reserve is compromised, the possibility of oocyte retrieval is still present if aggressive stimulation strategies are employed. In the context of SCD, patients are at risk for a two-hit effect: disease related diminished ovarian reserve and possible teratogenic and gonad toxic effects from decades long hydroxyurea treatment, underscoring the need for timely fertility preservation strategies prior to curative therapies (Singer et al., 2010).

4.4. Contraception and Gynecological Pathologies

The management of contraception and general gynecological complaints has to be intricately tailored in hematological patient groups to ensure that underlying pathologies are not exacerbated. Women suffering from bleeding disorders experience dysmenorrhea and hemorrhagic ovarian cysts at heavily elevated rates (up to 25% prevalence for hemorrhagic cysts). Hormonal therapies, particularly the LNG-IUS and COCs, play a vital role in the management of such patients (Kuo et al., 2022). These therapies not only provide highly reliable forms of contraception but also inhibit ovulation and thin the endometrium to protect against hemorrhagic complications. The LNG-IUS is particularly effective in providing a safety profile up to eight years, which is essential in resource-limited settings. On the other hand, among women with SCD, estrogen-based contraceptives are generally considered contraindicated because of the inherently increased thrombotic risk associated with the disease (Gracia et al., 2014).

This requires the strict use of progesterone-only contraceptives (e.g., progestin-only pills, medroxyprogesterone injectables or implants).

Despite the obvious medical recommendations, a globally documented phenomenon of underutilization of effective and long-lasting reversible contraception (LARC) among women with SCD has been documented, making them at a high risk for unplanned and high-risk pregnancy (Pecker & Kuo 2022).

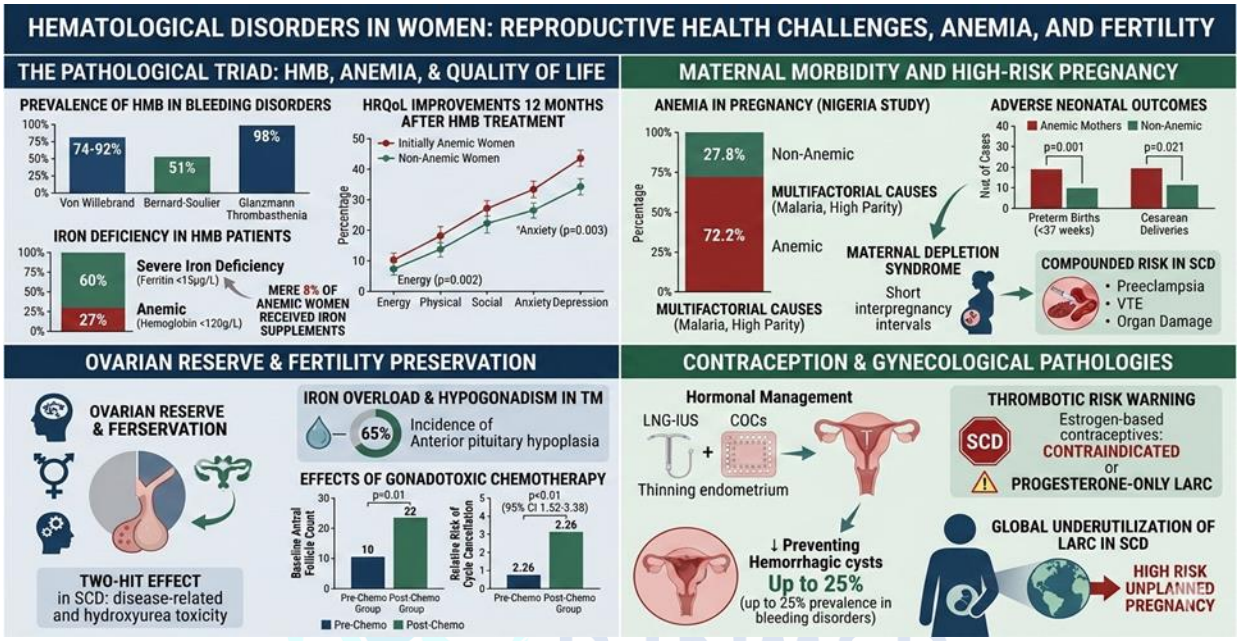

Fig. 01. Maternal Morbidity and High-Risk Obstetrical Outcomes

5. Comparative Analysis of Findings

A critical synthesis of the literature reveals that the divergent mechanisms of various hematological disorders that dictate reproductive health are highly distinct. For example, benign, acquired disorders such as IDA, which is caused by HMB, mainly manifest as a nutritional and mechanical deficit by Singer, S. T. (2010). In these disorders, the reproductive system is said to function normally but serves as a pathway for excessive blood loss, leading to fatigue, impaired fetal growth, and reduced HRQoL. In these disorders, appropriate medical interventions, such as IV iron, LNG-IUS, and antifibrinolytics, are known to result in immediate, robust, and complete improvements in life quality by Vega, O and Higa, (2010). By stark contrast, inherited disorders of hemoglobin (SCD, TM) and hematologic malignancies result in profound end-organ and endocrine damage. In TM, iron toxicity-mediated oxidative damage to the HPG axis results in profound anovulation and amenorrhea, which cannot be reversed by simply stopping bleeding. In SCD, the effects of chronic vaso-occlusion on the HPG axis delay the onset of puberty by 2-4 years, accelerate ovarian aging, and confer severe morbidity during pregnancy (Cedars et al., 2010). With regard to the impact of therapeutic interventions, there is a stark contrast between the universally therapeutic and grossly undertreated iron deficiency anemia in HMB and the inherent anti-fertility effects of the primary treatment for SCD and malignancies, respectively. Hydroxyurea and alkylating agents are universally anti-fertile (Cedars etal., 2010). This represents a stark paradox in which life-preserving therapy results in reproductive senescence. Lastly, with regard to the role of predictive markers of fertility, whereas classic markers of ovarian function, such as ratios of LH to FSH and estradiol, fail to accurately predict fertility in TM, antral follicle count remains a highly accurate and clinically relevant predictor of fertility in post-chemotherapy malignancy patients (Koliou et al. 2004).

6. Gaps and Limitations

Notwithstanding the notable improvements within the fields of haematology and reproductive

health, there are still important knowledge areas that require further exploration. One of the critical gaps in practice pertains to the treatment of iron deficiency anaemia (IDA) among women suffering from menorrhagia. Despite extensive research proving that there is a high prevalence of IDA in patients with menorrhagia based on objective haematological parameters such as serum iron, total iron binding capacity, and serum ferritin, there is a relatively low rate of appropriate iron treatment (Al-Buhairan & Oluboyede, 2001; Peuranpää et al., 2014). There seems to be a misconception among clinicians that the control of menorrhagia will automatically cure IDA, despite its chronicity and multifactorial aetiology, with no study investigating the rationale behind this phenomenon (Peuranpää et al., 2014).

The second major gap involves the evaluation of ovarian reserve among women with haemoglobinopathies. Although AMH and AFC have become established ovarian reserve measures among the general infertility population, the predictive validity of AMH and AFC as measures of ovarian reserve among women with thalassaemia major and SCD is inadequately investigated. For instance, Singer et al. (2010) have clearly noted that classical endocrine markers of fertility, such as LH and FSH, exhibit poor predictive validity regarding fertility outcomes among women with thalassaemia major. Notably, no study to date has assessed the relationship between AMH levels and pituitary iron deposition using MRI, which is surprising considering the established association between transfusional iron overload and hypogonadotropic hypogonadism among women with haemoglobinopathies (Skordis et al., 2004; Borgna-Pignatti et al., 2004). Finally, in the area of oncofertility, even though Senapati et al. (2014) showed promising rates of egg collection after aggressive gonadotropin stimulation in patients suffering from blood-related diseases, the lack of data in regard to the rate of fertility, birth rate, and quality of chromosome structure of embryos made of eggs collected after treatment of gonadotoxic chemotherapy is a significant issue, which makes evidence-based advice difficult (Klock et al., 2010; Lee et al., 2006; Dolmans et al., 2005). Additionally, the poor use of LARC methods by SCD female sufferers is a largely understudied aspect of socio-demographics and healthcare systems (Pecker & Kuo, 2022). Finally, the burden that reproductive health imposes on women suffering from inherited bleeding diseases, including von Willebrand disease or haemophilia carriers, has been poorly characterised. Existing research on this topic is mostly focused on developed countries (Plug et al., 2006; Kadir & James, 2009; Rodeghiero et al., 1987).

7. Future Perspectives and Recommendations

The nexus of haematology and women's reproductive healthcare is a subject area that continues to receive inadequate research attention in view of its practical importance. The way ahead calls for innovative and transformative strategies with particular emphasis on equity.

7.1 Aggressive Hematological Screening in Gynecology: There is a need to break the association of the treatment of menstrual bleeding and the treatment of the ensuing anemia. Rapid and highly assimilated iron therapy should be included in the immediate management of patients with HMB, rather than conservatively managing the condition and hoping for spontaneous resolution of the hematologic condition over a span of years (Ugwuja et al., 2009).

7.2 Standardization of ORT in Chronic Blood Disorders: In order to effectively manage and preserve fertility in patients with SCD and TM, ovarian reserve testing, such as measurement of AMH and AFC, should be included in the annual management of these patients, especially in the adolescent and adult population, to effectively manage and preserve fertility before the onset of profound follicular exhaustion (Ugwuja et al., 2009).

a) **Optimized Peripartum Co-Management:** Pregnancies in women with SCD, severe bleeding disorders, and profound IDA should only occur in highly specialized tertiary medical centers with immediate and unhindered access to hematologists and high-risk maternal-fetal medicine obstetricians around the clock

to prevent VTE, PPH, and vaso-occlusive crises (Ugwuja et al., 2009).

b) **Enhanced Preconception and Contraceptive Counseling:** Mandatory and routine implementation of reproductive life planning for women with bleeding disorders and IDA is of the essence. This includes intensified education on the safety and efficacy of progesterone-only LARC in thrombotic hematologic disorders, such as SCD, in addition to partner genetic screening via high-performance liquid chromatography prior to conception (Ugwuja et al., 2009).

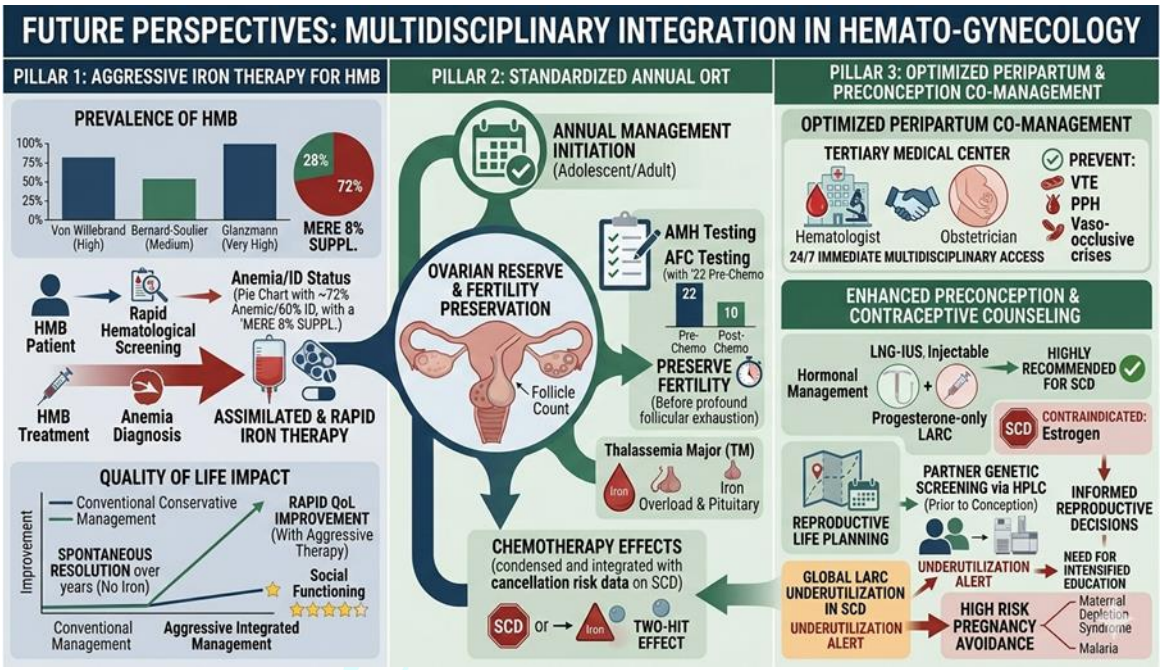

Fig. 02. Multidisciplinary integration in hemato-gynecology

8. Conclusion

The reproductive health of women is intricately, biologically and inextricably linked to their hematological health. From the omnipresent and extremely debilitating effect of iron deficiency anemia secondary to excessive menstrual blood loss to the alarming maternal and fetal mortality risk associated with sickle cell disease and bleeding disorders, hematological disorders have cast a long and ominous shadow over the entire spectrum of the reproductive health of women (Ames et al., 2007). Furthermore, the life-saving interventions used to treat hematological malignancies and severe hemoglobinopathies have had a devastating effect on ovarian reserve, creating a complex and urgent need for advanced fertility preservation techniques and endocrinological expertise (Singer et al., 2010). The body of current literature quite forcefully demonstrates that while the reproductive and hematological parameters are well-characterized individually, the overlap between the two is marred by a lack of timely interventions, underutilization of available predictive testing modalities (such as ORT) and a generally fragmented approach (Pecker & Kuo 2022). Improvement in the true quality of life, fertility potential, and lifespan of these patients will only be possible with a cohesive and aggressive approach to nutritional deficiencies, the anticipation and management of gonadal toxicities, and the provision of a robust and specialized approach to the overall reproductive experience (Ugwuja et al., 2009).

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