Leukemia in pregnancy: Diagnosis and therapeutic approach (Review)

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Abstract. The present study aimed to evaluate the epidemiological, diagnostic and therapeutic data of hematological malignancies in pregnancy. Leukemia in pregnancy is rare, and literature data are not extensive. Risk factors, epidemiology and pathogenesis of these diseases are not fully developed. Furthermore, there is a detailed report on the complications in pregnancy and the overall (per trimester) management of these diseases, specifically their treatment strategy. The possibility of achieving a future pregnancy in women with leukemia is described in the present study. The limited clinical research data currently available is mainly due to the inability to conduct randomized clinical trials for ethical reasons. Further research is needed, firstly due to the importance of these diseases for the pregnant woman and the fetus, and secondly, due to the continuous development of novel anticancer drugs that aim to improve the prognosis of these diseases.

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1. Introduction

Leukemia is defined by the unregulated proliferation and accumulation of immature precursors of white blood cells in bone marrow and peripheral blood. There are two types of leukemia: Acute and chronic, with acute lymphoblastic leukemia (ALL) being the most common category of acute leukemias. ALL requires immediate treatment due to the rapid accumulation of lymphoblasts. Chronic leukemia is characterized by excessive production of relatively mature but abnormal white blood cells, and includes chronic lymphocytic and myelogenous leukemia. Treatment in lymphocytic leukemia treatment is administered only to symptomatic patients, while in chronic myeloid leukemia (CML), therapy is offered in all cases (1).

The purpose of the present study was to analyze and describe how to manage the most common hematological malignancies, especially leukemias and lymphomas, during pregnancy. Although rare, occurring in ~1 in 75,000 to 100,000 pregnancies, the concurrent management of leukemia and pregnancy requires a careful balance to optimize outcomes for both the mother and the fetus. The physiological changes

in pregnancy can complicate the diagnosis of leukemia, as symptoms such as fatigue, anemia and thrombocytopenia overlap with normal gestational changes. The primary objective in treating leukemia during pregnancy is to achieve the best possible outcome for the mother while minimizing risks to the developing fetus. Chemotherapy is the cornerstone of leukemia treatment and can be administered during pregnancy, but the timing and choice of chemotherapeutic agents must be carefully considered. During the first trimester, the fetus is particularly vulnerable to teratogenic effects, thus posing a significant risk when administering chemotherapeutic agents. In the second and third trimesters, the risk of congenital malformations decreases, yet concerns about preterm labor, intrauterine growth restriction, and long-term developmental issues remain. The likelihood of achieving a future pregnancy is additionally described in women with hematological malignancies if they are receiving medication. The current study also analyzed the general characteristics of leukemias and lymphomas related to the epidemiology, pathophysiology, diagnosis, clinical appearance and treatment of these diseases. Acute myeloid leukemia (AML) constitutes 90% of all acute leukemias in adults. Intensive chemotherapy regimens and bone marrow transplantation can succeed in high cure rates, but they are rarely applicable, while recently targeted therapies were able to improve survival (1,2).

2. Methods

For the present study, articles published from 2013 to 2024 were reviewed. Relevant articles were identified through searches in the following databases: PubMed (https://pubmed.ncbi.nlm.nih.gov/), ScienceDirect (https://www.sciencedirect.com/), Cochrane Library (https://www.cochranelibrary.com/), Web of Science (https://www.webofscience.com/wos/), Embase (https://www.embase.com/) and Google Scholar (https://scholar.google.com/). To ensure comprehensive results, terms in Medical Subject Headings (https://www.nlm.nih.gov/mesh/meshhome.html) such as 'pregnancy', 'gestational', 'pregnant women', 'leukemia', 'lymphoma', 'metastasis', 'bone marrow' as well as 'chemotherapy' were searched in the international electronic database search. Boolean operators (AND & OR) were used to combine search terms and obtain comprehensive results. Additionally, references cited in the retrieved articles were examined to identify further relevant studies.

Inclusion and exclusion criteria. The inclusion criteria for the present study encompass prospective and retrospective studies aimed at investigating the association between maternal anemia during pregnancy and premature birth. The exclusion criteria were as follows: i) Non-related studies and duplicates; ii) studies involving preexisting leukemia or lymphoma; and iii) studies with unavailable full text.

Study selection. Initially, two researchers conducted the search process. Non-relevant articles were excluded by reviewing the title and abstract at each stage of the search. Full-text articles were then reviewed, and all studies pertaining to leukemia, lymphomas, as well as bone marrow metastasis during pregnancy were selected. The authors focused on review articles and meta-analyses, as these publications are crucial in literature searches. Their ability to synthesise extensive research, conserve time, deliver critical evaluations, and present comprehensive insights into a subject significantly aids in making informed and evidence-based decisions. In addition, in instances of rare types of leukemia, such as hairy cell leukemia, case reports were evaluated (Table I).

3. Acute myeloid leukemia

Pathophysiology of AML. The biology of AML is diverse, and is primarily characterized by the abnormal proliferation and differentiation of myeloid precursors within the bone marrow. AML is initiated by a clonal process originating from transformed hematopoietic stem cells, leading to clonal proliferation. Notably, this clonal proliferation can occur in individuals without any apparent health issues prior to the onset of leukemia (3).

Several factors distinguish age-related clonal hematopoiesis from pre-AML, including the number of mutations per sample, higher variant allele frequency, and mutations in specific genes such as i) DNA methyltransferase 3 alpha (DNMT3A), which encodes the enzyme DNA (cytosine-5)-methyltransferase 3 alpha, which is involved in establishing and maintaining DNA methylation patterns, playing a crucial role in gene expression regulation and cellular differentiation, ii) Tet methylcytosine dioxygenase 2 (TET2), which encodes the TET2 protein, which is involved in the process of DNA demethylation through the oxidation of 5-methylcytosine to 5-hydroxymethylcytosine, an important step in epigenetic regulation, iii) serine and arginine rich splicing factor 2 (SRSF2) which encodes a member of the serine/arginine (SR) protein family, which is essential for pre-mRNA splicing (3). The SRSF2 protein plays a critical role in the regulation of alternative splicing and the processing of pre-mRNA, and iv) additional sex combs like 1, transcriptional regulator (ASXL1), which is the gene that encodes the ASXL1 protein, is involved in chromatin remodeling and transcriptional regulation. This protein is part of the polycomb repressive complex, which plays a role in maintaining the transcriptional repression of genes involved in development. These distinctions are crucial for understanding the transition from clonal hematopoiesis to AML and guiding clinical management strategies (3). AML diagnosis traditionally involves morphology and cytogenetics, identifying translocations and recurrent cytogenetic abnormalities. Next generation sequencing panels and fusion partner agnostic sequencing are increasingly used for 4131428709AML diagnosis, providing information on mutations with prognostic and therapeutic implications. Somatic mutations play a crucial role in AML classification, diagnosis, prognosis and treatment decisions. Genes such as nucleophosmin 1 (NPM1), Fms related receptor tyrosine kinase 3 (FLT3) and CCAAT enhancer binding protein alpha (CEBPA) impact diagnostic subtyping and provide prognostic insights, especially in patients with a normal karyotype. The 2022 European LeukemiaNet classification includes mutations in 10 genes for adverse group assignment, and clinical genomic sequencing aids in evaluating patients at risk for myeloid malignancy (3). Assay sensitivity and mutation type determine suitability for measuring measurable residual disease (MRD), an area of active investigation (3).

Table I. Studies retrieved for conducting the review.

First author, year	Type of study	Summary	(Refs.)
Voulgaris *et al*, 2011	Review	Optimal patient care necessitates collaboration among multidisciplinary teams.	(5)
Thomas, 2015	Review	Although chemotherapy carries certain risks during the first trimester, it is acknowledged that it can be safely administered during the second and third trimesters.	(6)
Zhu *et al*, 2021	Review	In cases of acute leukemia diagnosed during the first trimester or late stage of pregnancy (>30 weeks), opting for elective termination or induced delivery before initiating chemotherapy may lead to improved maternal and fetal outcomes.	(7)
Ali *et al*, 2015	Practice guideline	For women diagnosed with AML during pregnancy, prompt treatment is crucial. Diagnosis in the first trimester often leads to poor pregnancy outcomes, with significant risks of spontaneous pregnancy loss. The decision of elective termination should be carefully discussed with the patient, weighing the reasons for and against. If AML is diagnosed beyond 32 weeks of gestation, delivering the fetus before starting chemotherapy may be considered. Between 24 and 32 weeks, the decision regarding fetal exposure to chemotherapy vs. risks of premature delivery must be balanced carefully.	(8)
Sanz *et al*, 2019	Review	In patients diagnosed APL, those with ATRA-sensitive variants should receive treatment combining ATRA with anthracycline-based chemotherapy. However, for patients with ATRA-resistant variants, the addition of ATRA is less effective, and management should follow approaches similar to those used for AML.	(13)
Santolaria *et al*, 2020	Systematic review	In APL, the likelihood of achieving CR and subsequent cure is generally very high and comparable to non-pregnant patients. However, fetal outcomes are closely tied to gestational age, with a notable increase in abortion rates during early pregnancy stages.	(14)
Ticku *et al*, 2013	Case report and review	ALL may be treated with HyperCVAD during the third trimester of pregnancy.	(19)
Vlijm-Kievit *et al*, 2018	Case reports	In acute lymphoblastic leukemia, the placenta typically acts as a barrier preventing the transfer of maternal leukemia cells to the fetus. In rare instances where this barrier fails, allowing leukemia cells to pass to the fetus, the infant's immune system may mount a response to clear the leukemia cells.	(23)
Abruzzese *et al*, 2020	Review	If pregnancy is suspected or confirmed in a female CML patient, it is generally recommended to interrupt TKI treatment. For patients with a high tumor burden (≤MR2), management should parallel that of newly diagnosed or recent CML cases, regardless of whether they have been on treatment for less than or more than 3 years. This approach typically involves a combination strategy using IFN and TKI therapy timed appropriately.	(31)
Soverini *et al*, 2016	Review	In the context of CML, in subsequent MR reports, it is crucial for the pathologist or molecular biologist to clearly state whether the sample is suitable for MR evaluation and to specify whether the MR level indicates an optimal response, a warning, or a failure. If the sample is assessable, they should specify the exact MR level achieved. In instances where there are discrepancies in MR results compared to previous assessments, fluctuations in BCR-ABL1 transcript levels without loss of MMR, or borderline findings, it is recommended that the pathologist or molecular biologist advise	(32)

Table I. Continued.

First author, year	Type of study	Summary	(Refs.)
		on the necessity for resampling and verification of results before making any clinical decisions.	
Luttwak *et al*, 2021	Review	Aggressive lymphoproliferative diseases in pregnant patients have the potential for cure. In recent years, new treatments have been introduced that have not been studied in pregnant or breastfeeding women. Rituximab, an anti-CD-20 monoclonal antibody, can be safely given during the second and third trimesters of pregnancy. When considering other treatments where the effects on the fetus are unknown or could be harmful, a personalized approach should be taken. This involves shared decision-making between the patient and her healthcare team.	(38)
Daver *et al*, 2013	Case report	A positive result was achieved in a pregnant patient with HCL who underwent treatment with a monoclonal antibody (rituximab) followed sequentially by a purine analogue (cladribine).	(39)
Gurevich-Shapiro and Avivi, 2019	Review	If HL is diagnosed in the first trimester and immediate treatment is not urgent, therapy should be deferred until the second trimester. Bridging therapy with vinblastine or corticosteroids can be considered during the first trimester if necessary. ABVD is the preferred chemotherapy regimen during pregnancy. It can be safely administered during the second and third trimesters, once the placenta is well-developed and fetal organogenesis is mostly complete. Radiation therapy is generally avoided throughout pregnancy due to the potential risks to the fetus. In select cases of localized supradiaphragmatic disease where radiation therapy might be deemed necessary, it should be performed with careful consideration and appropriate shielding techniques to minimize fetal exposure. Treatment for newly diagnosed NHL during pregnancy varies depending on the subtype and aggressiveness of the lymphoma. Indolent lymphoma: For indolent NHL, a strategy of watchful waiting until delivery can often be employed. In cases where treatment is necessary during pregnancy, a short course of corticosteroids can be used as bridging therapy to manage symptoms. Aggressive lymphoma: R-CHOP is considered the standard regimen for aggressive NHL. It can be safely administered beyond the first trimester of pregnancy. CNS prophylaxis with high-dose methotrexate is contraindicated before week 20 of pregnancy and is generally not recommended during pregnancy due to potential fetal harm. Highly aggressive lymphoma (e.g. Burkitt's lymphoma): Burkitt's lymphoma requires immediate treatment with intensive chemotherapy regimens that often include antimetabolites. In cases of highly aggressive NHL, prompt termination of pregnancy may be recommended followed by initiation of intensive chemotherapy. The decision to terminate pregnancy and start chemotherapy is based on the urgency of treatment and the potential risks to both the mother and the fetus.	(47)

Table I. Continued.

First author, year	Type of study	Summary	(Refs.)
Ciccarone *et al*, 2023	Observational study	Based on the results obtained from hormonal measurements and follicle echography, it appears that the adverse impact of ABVD on fertility is temporary. However, by contrast, more intensive therapies may have the potential to cause more significant and enduring harm to fertility.	(49)
Câmara and Brandão, 2023	Systematic review and meta-analysis	Recent patents have been published concerning the use of monoclonal antibodies in the treatment of NHL. These antibodies are associated with adverse effects such as neutropenia (grade 3-4) and thrombocytopenia.	(53)
Pirosa and Peccatori, 2023	Review	Hodgkin lymphoma and pregnancy: ABVD regimen is considered safe if administered after the 13th week of pregnancy. NHL and pregnancy: Indolent NHLs, a watchful waiting approach is often considered. Indolent NHLs grow slowly and may not require immediate treatment. Aggressive NHLs, treatment approach depends on the timing of diagnosis relative to pregnancy. If diagnosed in the first trimester, termination of pregnancy might be considered due to potential risks of aggressive treatment on fetal development. If diagnosed after the 13th week, a standard R-CHOP regimen can be considered safe. R-CHOP is a common regimen for aggressive NHL. New anti-lymphoma drugs and pregnancy: Data on potential fetotoxicity (ability to cause harm to the fetus) of newer anti-lymphoma drugs are limited. This suggests caution is needed when considering these drugs during pregnancy, and decisions would likely be made on a case-by-case basis weighing potential risks to the fetus against benefits to the mother.	(55)
Evens *et al*, 2013	Review	In lymphomas, standard combination chemotherapy, which typically excludes antimetabolite drugs, can be administered safely after the first trimester of pregnancy. This timing (around 13 weeks gestation and beyond) is chosen to minimize potential risks to fetal development during the critical early stages.	(57)
Krashin and Lishner, 2016	Review	Several small-scale studies indicate that the outcomes for infants born to mothers with leukemia may not show significant differences compared to infants born to mothers without health complications. The existing literature on the long-term effects of chemotherapy for leukemia is constrained and predominantly relies on retrospective data. A comprehensive follow-up study, spanning an average of 18.7 years, involving 84 children born to mothers with hematological malignancies, including 29 with acute leukemia, documented normal physical, neurological, and psychological development among these children. The incidence of malignancy in this cohort was comparable to that observed in the general population, and notably, 12 of these children later became parents themselves.	(77)

AML, acute myeloid leukemia; APL, acute promyelotic leukemia; ATRA, all-*trans* retinoic acid; CR, complete remission; ALL, acute lymphoblastic leukemia; HyperCVAD, cytoxan, vincristine, adriamycin, dexamethasone; CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor; MR, molecular response; BCR, B-cell receptor; MMR, major molecular response; HCL, hairy cell leukemia; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; NHL, non-Hodgkin lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone; CNS, central nervous system.

Risk factors of AML. Inherited conditions such as Fanconi anemia and Diamond-Blackfan anemia, along with genetic mutations in the germline, namely runt-related transcription factor 1 (RUNX1), CEBPA and GATA binding protein 2 (GATA2), increase the risk of AML. Alterations in the RUNX1 gene are linked to both benign and malignant blood disorders, with a notable impact on megakaryocyte and myeloid lineages. Smoking, chemicals, prior chemotherapy, radiotherapy and another myelodysplastic syndrome are associated with AML (3,4).

General therapeutic approach for AML. Chemotherapy (cytarabine and anthracycline) and bone marrow transplantation are offered for young patients, while targeted therapies are the main therapies used for the elderly (3).

AML in pregnancy. The incidence of leukemia in pregnancy ranges from 1 in 75,000 to 1 in 100,000 pregnancies, with AML being the most common subtype. Acute leukemias appear more often during the second and third trimesters of pregnancy, while only 23% of them are diagnosed in the first trimester. Their treatment should begin immediately after diagnosis, and termination of pregnancy is mainly recommended in the first trimester. Although the risk of teratogenicity from chemotherapy is negligible in the second and third trimesters, the severity of the disease and treatment complications make the termination of pregnancy necessary (5).

Clinical presentation of AML in pregnancy. Pregnancy often results in a delay in diagnosis. Because the early symptoms are non-specific, the diagnosis is mainly made during the second and third trimesters. Unspecific symptoms such as fatigue, weakness, dyspnea and pallor are usually physiological changes occurring during pregnancy. The physiological changes associated with pregnancy, such as anemia of pregnancy, leukocytosis or gestational thrombocytopenia, are typically present in AML. Furthermore, recurrent infections and bleeding can reflect bone marrow failure (6).

Diagnosis of AML in pregnancy. The diagnosis of AML is often complicated during pregnancy. Laboratory findings such as neutropenia, anemia, thrombocytopenia, thrombosis or coagulation disorders could appear. The presence of blasts in peripheral blood results in a possible diagnosis and is confirmed with bone marrow biopsy, while immunophenotype of blasts and cytogenetics with genetic analysis (FLT3, IRD, TKD and NPM1 mutations) are imperative for risk stratification (5).

Management of AML in the first trimester of pregnancy. Complications of AML include limitation of endometrial development, abortion and perinatal death. Due to these consequences, pregnancy termination is suggested when diagnosis of AML is established in the first trimester (6).

Management of AML in the second and third trimesters of pregnancy. Chemotherapy and pregnancy maintenance are recommended between the 13 and 24th weeks, while between the 24 and 34th weeks the danger of prematurity overweighs that of chemotherapy. When AML appears after the 32nd week, labor induction is suggested, and chemotherapy is administered after labor. The preferred chemotherapeutic schemes in the second and third trimesters are anthracyclines. In pregnancy, doxorubicin is mainly used, whereas idarubicin, as a lipophilic molecule, crosses the placenta and is therefore not recommended. It has been shown that anthracyclines are involved in fetal cardiotoxicity (7). Thus, regular fetal ultrasound during treatment is suggested. Experience of cytarabine administration during pregnancy is limited. However, cytarabine is involved in fetal limb dysplasia, especially in the first trimester, and it is responsible for pancytopenia, endometrial death, limitation of endometrial development and neonatal death (8).

4. Acute promyelocytic leukemia

Pathophysiology of acute promyelocytic leukemia (APL). APL is characterized by the accumulation of immature granulocytes and is caused by a chromosomal translocation of the first intron of α-receptor of retinoic acid (RARα) on chromosome 17 and promyelocytic leukemia (PML) gene on chromosome 15. PML and RARα fusion leads to the expression of a dysfunctional hybrid protein, which inhibits the differentiation of promyelocytes into mature granulocytes (8,9).

Risk factors of APL. Advanced age, chemical solvents, prior myelodysplastic syndromes and germline mutations contribute to the development of APL (9).

General therapeutic approach for APL. Targeted therapy with all-*trans* retinoic acid (ATRA), the prodromal form of vitamin A, in combination with chemotherapy is the classic regimen termed ATRA and idarubicin (AIDA), offering a cure in >90% of patients. Since 2013, a drug combination of arsenic trioxide with ATRA can offer higher cure rates and fewer relapses compared to AIDA, and consists of a chemo-free therapeutic approach to the disease (10).

APL in pregnancy. APL is a rare comorbidity during pregnancy, with a low prevalence of 1 in 75,000 to 1 in 100,000 pregnancies, the majority of which are cases of AML (10,11).

Clinical presentation of APL in pregnancy. Recurrent infections, fatigue and hemorrhagic risk are associated with APL, while petechiae and coagulopathy are common clinical manifestations (11).

Diagnosis of APL. Diagnosis is based on bone marrow biopsy and detection of the characteristic PML/RARα chimeric oncoprotein. Morphology is usually helpful with the presence of promyelocytes, which are characterized by the presence of Auer rods in peripheral blood samples (12).

Management of APL in the first trimester of pregnancy. Treatment in pregnancy is administered following the cooperation of specialized gynecologists-obstetricians, hematologists and neonatologists. APL causes coagulation disorders that can complicate gestation. For this reason, regular check-up is mandatory. As for the therapeutic approach, it depends on the trimester in which the disease is diagnosed. In the first trimester, termination of pregnancy and prompt induction

therapy are advised. The standard induction chemotherapy is the '7+3' regimen, which includes continuous infusion of high-dose cytarabine for 7 days in combination with anthracycline infusion during the first 3 days. These are teratogenic if administered during organogenesis. In the first trimester, chemotherapy is recommended in women who refuse terminating the pregnancy. ATRA should be avoided in the first trimester because it increases the risk of abortion, and enhances the possibilities of cardiovascular fetal malformation and prematurity. Furthermore, it can lead to microphthalmia, microcephaly, hearing loss and mental disturbances in the newborn. The exclusive administration of chemotherapy results in a lower response to therapy, smaller free-of-disease intervals and a higher number of relapses. Daunorubicin is the anthracycline of choice in the first trimester, since it may induce less fetal toxicity, and ATRA can be added to treatment during the second and third trimesters. Arsenic trioxide is teratogenic and should be avoided in all three trimesters of pregnancy (13,14).

Management of APL in the second and third trimesters of pregnancy. During the second and third trimesters, ATRA and chemotherapy can exclusively be administered after childbirth. Another choice is the coadministration of ATRA with chemotherapy during pregnancy. This coadministration offers increased cure rates but it is associated with increased risk of abortion, prematurity, neonatal neutropenia and sepsis. Monotherapy with ATRA has the same percentages of disease recession but increases the risk of relapse and causes leukocytosis. For this reason, in cases of monotherapy with ATRA, regular check-ups with PCR and check-ups for disease relapse are necessary. The preferred method of delivery is vaginal, due to the lower risk of hemorrhage (15).

5. Acute lymphoblastic leukemia

ALL is an aggressive hematological tumor of lymphoid origin that causes immature lymphoblasts to proliferate uncontrollably in the bone marrow, blood and tissues. B-cell ALL is more common and is characterized by the presence of the Philadelphia chromosome and the B-cell receptor (BCR)/ABL (p190) oncoprotein, which can be targeted with tyrosine kinase inhibitors (TKIs). If it remains untreated, it can lead to mortality rapidly (16).

Pathophysiology of ALL. ALL is considered to occur after DNA damage. As a result, abnormal lymphocytes and their progenitors undergo uncontrolled proliferation and spread throughout the body, resulting in the replacement of the bone marrow and other lymphoid organs (17). Immunophenotyping using multi-channel flow cytometry (MFC) has become the standard procedure for diagnosing and subclassifying ALL. Additionally, it serves as a valuable tool for detecting and monitoring MRD. According to the European Group for the Immunological Characterization of Leukemias consensus, blast cells are considered positive for a given monoclonal antibody if they exhibit a threshold of 20% expression, except for markers such as MPO, CD3, CD79a and TdT, which are deemed positive at 10% expression. The EuroFlow consortium has developed novel MFC strategies to ensure the accuracy and reproducibility of diagnostic tests. In total, 75-80% of adult ALL cases are of B-cell lineage, while 20-25% belong to the T-cell lineage (18).

Risk factors of ALL. Genetic syndromes, Down syndrome, severe combined immunodeficiency, genetic mutations in the GATA3 gene, prior chemotherapy and radiotherapy are related to ALL (19).

General therapeutic approach for ALL. Intensive chemotherapy regimens [hyperfractionated cyclophosphamide, vincristine, doxorubicin (adriamycin) and dexamethasone or gemtuzumab ozogamicin, mitoxantrone, cytarabine (cytosine arabinoside), liposomal daunorubicin (GMAL)] and intrathecal central nervous system (CNS) prophylaxis is the mainstay of treatment. Prednisone, vincristine, anthracyclines, methotrexate and aracytin are commonly used. Other drugs such as L-asparaginase, cyclophosphamide and rituximab in $CD20^+$ ALL can be used as well (19). Relapse of the disease is usual, but bone marrow transplantation after bridging therapy with bispecific antibodies can be employed as salvage treatment (20). The technology of chimeric antigen receptor (CAR) T cells with chimeric receptors against CD19 provides another opportunity for remission in patients with B-ALL.

ALL in pregnancy. Studies on the coexistence of ALL in pregnancy are limited because it affects 1.3 in 100,000 gestations (20,21).

Clinical presentation of ALL in pregnancy. Clinical presentation includes fatigue, lethargy, headache, vomiting, hemorrhage, bone pain, joint pain, weight and appetite loss, as well as liver, spleen and lymph node enlargement, in addition to edema of the lower limbs and abdomen, metabolic disorders such as hyperuricemia, CNS paralysis due to malfunction, confusion, fever and susceptibility to infections (21).

Diagnosis of ALL in pregnancy. The presence of lymphoblasts in the complete blood count and peripheral blood smear are indicators of disease. Diagnosis is confirmed with a bone marrow biopsy. Cytogenetics of bone marrow samples direct the prognosis and treatment, especially in patients with the Philadelphia chromosome (22).

Management of ALL until the 20th gestational week. Pregnancy does not change the course of the disease, but a delay in treatment can adversely affect the outcome. Thus, when ALL is diagnosed in pregnancy, immediate treatment is recommended. The majority of protocols advocate the use of methotrexate, even though methotrexate has been reported to cause fetal aminopterin syndrome (cranial dysostosis and micrognathia). If ALL appears before the 20th gestational week, then pregnancy termination is suggested (23).

Management of ALL after the 20th gestational week. Prednisone is recommended for 1-2 weeks before the initiation of chemotherapy. Preferred chemotherapeutic agents include cytarabine, cyclophosphamide, anthracyclines, vincristine and steroids. Methotrexate is recommended only in the third trimester. Administration of chemotherapy in the last weeks of

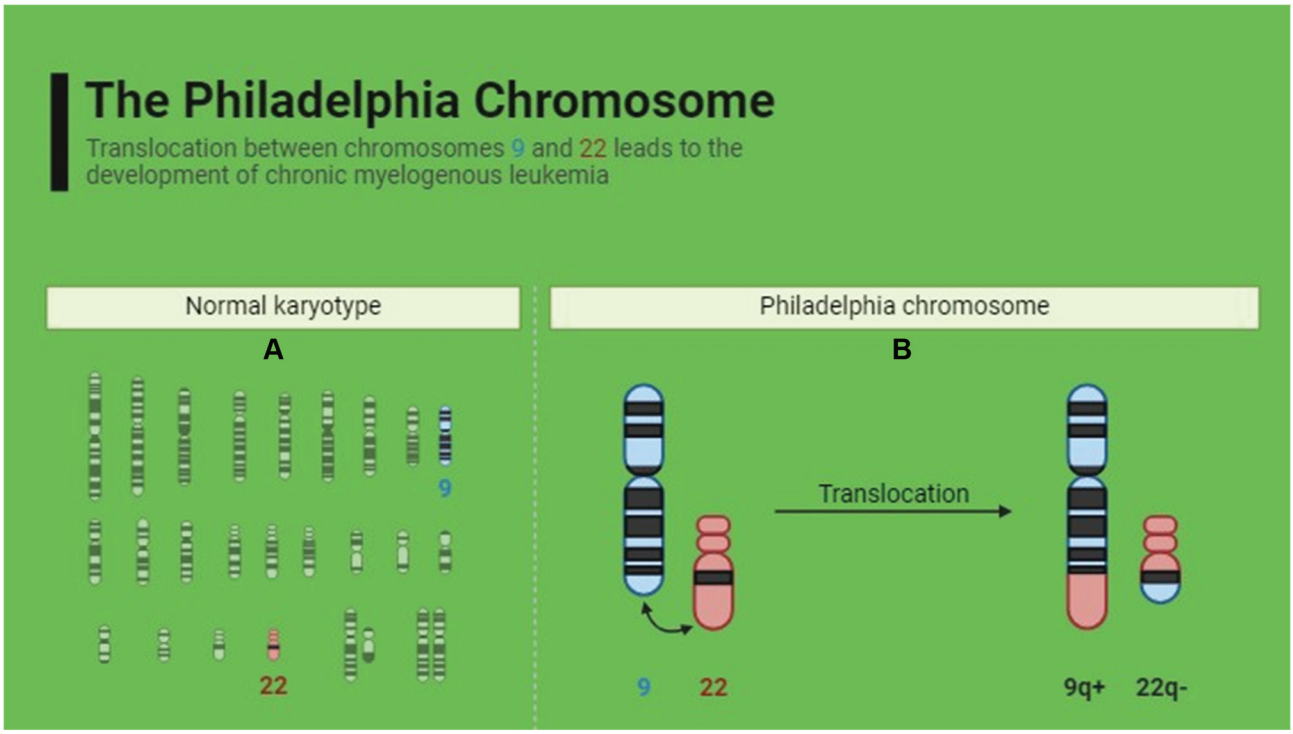

Figure 1. Normal karyotype vs. Philadelphia chromosome. The figure illustrates the distinct chromosomal alterations between the normal karyotype and the Philadelphia chromosome. (A) Normal karyotype representing the typical chromosomal arrangement found in healthy individuals, with chromosomes 9 and 22 shown in their intact, separate states. (B) Philadelphia chromosome is depicted as the abnormal chromosomal configuration resulting from a reciprocal translocation between chromosomes 9 and 22, leading to the fusion of the BCR and ABL genes. This fusion gives rise to the oncogenic BCR-ABL fusion protein, implicated in diseases such as chronic myeloid leukemia. BCR, B-cell receptor.

pregnancy is not recommended because it increases the risk of infections and hematological malignancies in newborn. After the 32nd gestational week, induction of labor is suggested to avoid fetal pancytopenia (23).

6. Chronic myeloid leukemia

CML. CML comprises 8% of all leukemia cases in the UK, and it appears most frequently during the sixth decade of life. CML is characterized by the presence of the Philadelphia chromosome t (9:22), leading to the excessive production of white blood cells in the bone marrow (24).

Pathophysiology of CML. The pathophysiology of CML involves a genetic exchange between chromosomes 9 and 22, resulting in the fusion of the BCR gene from chromosome 22 with the ABL gene from chromosome 9. This translocation forms the Philadelphia chromosome, which generates a novel hybrid chimeric oncoprotein (24), as shown in Fig. 1. Reverse transcription-quantitative PCR (RT-qPCR) analysis of BCR-ABL1 is the most sensitive method for detecting and monitoring abnormal fusion transcripts associated with certain leukemias. This analysis can be performed on peripheral blood or bone marrow samples. Unless there are specific clinical indications, it is generally not necessary to obtain bone marrow specifically for molecular testing (24).

Risk factors of CML. Exposure to ionizing radiation, advanced age and male sex may be associated with the development of CML (25).

General therapeutic approach for CML. TKIs, leukapheresis and interferon-α (INF-α) are used for the treatment of CML, while marrow transplantation is rarely used (26).

CML in pregnancy. CML constitutes ≤10% of all leukemias during pregnancy, with an annual incidence of 1 in 100,000 pregnancies. Its diagnosis during pregnancy is complicated. The disease is usually diagnosed in the second and third trimesters, while its progression is not affected by pregnancy (26).

Clinical presentation of CML in pregnancy. There are three phases of CML: Blast crisis, accelerated and chronic. A total of 90% of patients with CML are diagnosed during the chronic phase. If left untreated, CML progresses to the accelerated phase or the blast crisis phase. Blast crisis represents the ultimate phase of CML and is characterized by blast cells constituting >20% of total white blood cells (27). Prompt treatment is crucial for achieving remission and preventing progression to advanced stages. The clinical presentation of CML depends on the stage of the disease. Most patients diagnosed in the chronic phase are usually asymptomatic. If symptoms appear, these include right and left hypochondriac pain (due to hepatosplenomegaly), low-grade fever and night sweats. Patients in the accelerated stage have an increased risk of hemorrhage, while patients in the blast crisis phase have joint pain, fever and bone marrow fibrosis (28).

Diagnosis of CML in pregnancy. Suspicion of the disease is based on increased numbers of neutrophils, basophils and eosinophils in complete blood count. Bone marrow biopsy

confirms the diagnosis. The common translocation between chromosomes 9 and 22 is confirmed by cytogenetic analysis, while the detection of BCR-ABL genes is performed with hybridization or PCR (29).

Therapeutic approach for CML in pregnancy. The therapeutic approach for CML includes leukapheresis, chemotherapy, INF-α and TKIs. However, the use of TKIs in the first trimester of pregnancy appears to lead to abortions and fetal anomalies such as craniosynostosis, hypoplastic lungs, double kidneys, cerebellar hypoplasia, scoliosis, polydactyly and premature closure of skull bones (30). There are not sufficient data on the safety of TKIs in the second and third trimesters. In the first trimester, for the safety of the fetus, leukapheresis is only suggested. Leukapheresis and INF-α are the safest therapeutic options in the second and third trimesters of pregnancy, while TKIs are a possible therapeutic option during the third trimester (31). Professional advice and follow-up from specialized oncologists-hematologists and gynecologists are recommended for the potential maternal effects from the termination of therapy and the potential dangers for the fetus due to therapy. Full administration of treatment should be stopped 10 months before conception and continued after delivery. Follow-up of the BCR-ABL gene is monthly recommended, and treatment must be administered if BCR-ABL increases >1% (32).

7. Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL). CLL is the most common type of leukemia in Western countries, with a positive association with age (usually diagnosed at ≥50 years of age) and male sex. In CLL, the bone marrow produces a large number of B lymphocytes. CLL is related to genetic mutations and epigenetic changes (33).

Pathophysiology of CLL. CLL is characterized by the clonal expansion of $CD5^+CD23^+$ B cells in blood, marrow and lymphoid tissues. Additionally, recurrent genetic lesions are implicated in CLL pathogenesis. Furthermore, attention has been focused on BCR and chemokine receptors that help CLL cells to home to lymphoid tissues, resulting in establishing a microenvironment for the development of leukemia (33). Flow-cytometric demonstration of the typical immunophenotype is essential for diagnosing CLL. CLL is characterized by a specific immunophenotype, which includes the expression of CD5, CD19, dim CD20, dim CD22, CD23, bright CD43, dim CD45, dim-to-negative CD79b, dim CD81, CD200 and dim monoclonal surface immunoglobulin (Ig). This distinct immunophenotype enables a definitive diagnosis of CLL and helps exclude other types of leukemia or lymphoma (33).

Risk factors of CLL. Known risk factors of CLL are family history, autoimmune diseases, exposure to pesticides and insecticides, and hepatitis C infection (34).

General therapeutic approach for CLL. If symptoms and treatment indications are absent, follow-up is only recommended. Depending on the stage, genetic features and clinical characteristics of the disease, pharmacological options include chemoimmunotherapy with an anti-CD20 monoclonal antibody or targeted therapies with BTK or BCL2 inhibitors. which can achieve disease control (35).

CLL in pregnancy. CLL in pregnancy is extremely rare and can present with cytopenia, which leads to an increased risk of infections and bleeding. For this reason, erythrocyte and platelet transfusions are necessary, with desirable hemoglobin values >10 g/dl and platelet values >50,000/μl. CLL in pregnancy is related to diabetes mellitus, especially in women who receive corticosteroids and in intrauterine growth restriction (36).

Clinical presentation of CLL in pregnancy. CLL is mainly asymptomatic, but with disease progression, painless lymphadenopathy, fever, fatigue, weight loss, anemia and splenomegaly appear. Patients are vulnerable to infections due to hypogammaglobulinemia and can develop autoimmune hemolytic anemia (36).

Diagnosis of CLL in pregnancy. Patients with swollen lymph nodes may be suspected of having the illness. In a peripheral blood smear, 'smudge cells' or 'basket cells' are apparent, and lymphocytosis manifests in a complete blood count. The primary basis for diagnosis is the presence of pathogenic B lymphocytes, which are clonal and genetically identical cells with surface expression of CD5 and CD23 molecules, in blood, bone marrow and tissues. Therefore, to diagnose CLL, peripheral smear microscopical inspection in conjunction with flow cytometric analysis of B lymphocytes (which verifies the clonality of these cells and highlights the expression of molecules on their cellular surface) is required. Imaging analysis, including computed tomography, completes the diagnosis of the disease. Confirmation of the diagnosis is established with immunophenotype of peripheral blood, while bone marrow biopsy is rarely required (37).

Therapeutic approach for CLL in pregnancy. Few cases of pregnant women with CLL (34) have been reported in the literature, so there are no leading directions. This results in the personalization of management of patients. Follow-up is suggested in most cases, without treatment until labor if the disease is not progressive. The therapeutic approaches in pregnancy are mainly related to complications of the disease. The patient should be examined systematically with physical examination, blood tests, follow-up of the fetus and ultrasound of lymph nodes. If therapy is needed, chlorambucil is preferred after the 15th gestational week because it is related to fetal abnormalities if received in the first trimester (35). Rituximab belongs to Pregnancy Category C according to the Food and Drug Administration (FDA) of the USA and is contraindicated in pregnancy. Pregnancy should be avoided if the patient is treated with rituximab until 12 months after the last dose. Complications of the treatment in the second and third trimesters are neonatal lymphopenia and reduction of B-lymphocytes. In addition, cladribine belongs to Pregnancy Category D according to the FDA, and is not recommended in pregnancy (36). CLL does not affect fertility and is not an inhibiting factor for pregnancy progression. Family planning and consultation are suggested if a patient receives or will receive pharmacological treatment, since numerous therapeutic agents

used for the treatment of CLL are contraindicated during pregnancy. Cooperation of a hematologist, gynecologist and the patient is useful during pregnancy (36,37). Ibrutinib is considered teratogenic because it causes heart malformation in pregnant rats and its use is not recommended during pregnancy as it belongs to Pregnancy Category D. Furthermore, Bruton's tyrosine kinase inhibitors can cause severe hypoglobulinemia in the fetus and severe immunodeficiency (38).

8. Hairy cell leukemia

Hairy cell leukemia (HCL) in pregnancy. HCL exhibits a unique immunophenotype characterized by staining with antibodies. In HCL, the cells typically show negativity for CD5, CD10 and CD23. Conversely, they display abnormally high expression of CD20, CD22, CD11c and CD25. Furthermore, HCL cells are positive for CD103 and CD123. This distinctive immunophenotypic profile aids in the diagnosis and differentiation of HCL from other leukemias and lymphomas (39).

Therapeutic approach for HCL in pregnancy. HCL is not treated unless excessive cytopenia symptomatic splenomegaly, recurrent infections, extra lymphatic involvement, autoimmune complications and/or progressive deterioration of the disease appear. Purine analogues, mainly cladribine, are widely used as first-line treatment, with percentages of disease eradication of 76-80% (39). Purine analogues belong to Pregnancy Category D due to their teratogenic effects and fetal mortality, but there are not sufficient data on the use of cladribine in pregnancy. INF-α is used for the treatment of HCL. Pregnant women in which INF-α was administered, had non-complicated pregnancy and physiological development of the child after labor. Splenectomy is a treatment of choice during the second trimester of pregnancy. In the medical literature, 4 cases of pregnant women were reported in which splenectomy was performed, and 2 of them needed cladribine after labor (39). Monoclonal antibodies, mainly rituximab, have been used in pregnancy for the treatment of acute HCL. As aforementioned, rituximab belongs to Pregnancy Category C, and its use in pregnancy slightly increases the risk of premature labor (40). Types, pathophysiology, risk factors and treatment of leukemias in pregnancy are summarized in Table II.

9. Lymphomas

Lymphomas in pregnancy diagnosis therapeutic approach. In the present review epidemiological, diagnostic and therapeutic data on lymphomas and multiple myeloma (MM) in pregnancy are presented. The current study mainly focuses on their management during pregnancy per trimester, the possibility of future pregnancy in women affected by lymphoma or MM, and the association between the therapy for these diseases and the danger of future infertility. It must be emphasized that the data and conclusions are based on the results of small-group cases of pregnant women that have been reported in the literature. Thus, further research in the field of hematological malignancies and pregnancy is necessary to validate the results. The term 'lymphoma' refers to a tumor that develops from immune system cells called lymphocytes (T or B cells), with B lymphocyte-derived lymphomas being more prevalent. Hodgkin and non-Hodgkin lymphomas are the two primary forms of lymphomas (41).

Hodgkin lymphoma (HL). HL is a tumor that arises from B-cell lymphocytes. The disease is characterized by the appearance of symptoms in advanced stages. HL appears more often in two age groups: 15-35 and >55 years of age (41).

Pathophysiology of HL. One type of cancer that affects the lymphatic system and is typically detected in the lymph nodes is HL. Large cells known as Reed-Sternberg (RS) cells are a hallmark of HL, which often begins in the lymph nodes and occasionally invades other organs (42).

Risk factors of HL. The risk factors of HL include male sex, age (15-40 and >55 years of age), positive family history, history of infectious mononucleosis, immunosuppression, extended use of growth hormone and exposure to exotoxins (43).

General therapeutic approach for HL. Patients at the early stage of the disease are treated with radiotherapy or chemotherapy, while patients at the advanced stage are treated with chemotherapy. The most known chemotherapy treatment is the doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) scheme. In addition, there are other chemotherapeutic schemes such as the bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone (BEACOPP) regimen. In advanced disease stages, the addition to the doxorubicin, vinblastine and dacarbazine (AVD) regimen of brentuximab vendotin, an anti-CD30 monoclonal antibody conjugated with a toxin that inhibits cell mitosis, has recently been approved as first-line therapy of HL (38).

HL in pregnancy. In pregnancy, the incidence of HL ranges between 1:1,000 and 1:3,000 (44).

Clinical presentation of HL in pregnancy. One of the most common features of HL is the painless enlargement of ≥1 lymph nodes. The lymph nodes appear edematous during clinical examination, while B symptoms (fever >38˚C, weight loss >10% in 6 months and night sweats) characterize this lymphoma (45).

Diagnosis of HL in pregnancy. Pregnancy-related HL is the sixth most common malignancy. RS cells, which are large cells expressing CD30 and CD15 antigens on their surface, are what define HL, and their presence is required for the diagnosis of HL. Diagnosis of the disease is accomplished by lymph node biopsy. Concerning the imaging methods used for staging, computed tomography (CT) and positron emission tomography (PET) scans are not used, while magnetic resonance imaging (MRI) and abdominal ultrasound are the most common methods (46).

Therapeutic approach for HL in the first trimester. If HL is diagnosed in the first trimester, delay of the treatment is preferred, since the fetus can be affected by chemotherapy during the stage of organogenesis. In case of aggressive lymphomas, termination of pregnancy is suggested, but if a woman does not wish to terminate the pregnancy, immediate

Table II. Types, pathophysiology, risk factors and treatment of leukemias in pregnancy.

Type of leukemia	Pathophysiology	Risk factors	Treatment
Acute myeloid leukemia	Accumulation of blasts in the bone marrow	Inherited conditions such as Fanconi and Diamond-Blackfan anemias; genetic mutations in the germline, namely RUNX1, CEBPA and GATA2 genes; epidemiological factors such as smoking and chemical exposure; prior chemotherapy, radiotherapy; and myelodysplastic syndromes	Termination of pregnancy is mainly recommended in the first trimester. Risk of teratogenicity is negligible in the second and third trimesters. The preferred chemotherapeutic schemes in the second and third trimesters are anthracyclines, especially doxorubicin.
Acute promyelocytic leukemia	Accumulation of immature granulocytes-chromosomal translocation involving the α-receptor of retinoic acid on chromosome 17 and the PML gene on chromosome 15; and dysfunctional hybrid protein, which interferes with the normal differentiation of promyelocytes into mature granulocytes	Advanced age, chemical solvents, prior myelodysplastic syndromes and germline mutations	Daunorubicin is the anthracycline of choice in the first trimester, while coadministration of all-*trans* retinoic acid and chemotherapy is recommended in the second and third trimesters
ALL	Damage to DNA, which causes abnormal lymphocytes and their progenitors to undergo uncontrolled proliferation and spread throughout the body, leading to the replacement of the bone marrow and other lymphoid organs. B-cell ALL is more common and is manifested by the presence of the Philadelphia chromosome and the BCR/ABL (p190) oncoprotein	Genetic syndromes, Down syndrome, severe combined immunodeficiency, genetic mutations in the GATA3 gene, and prior chemotherapy and radiotherapy	If ALL appears before the 20th gestational week, pregnancy termination is suggested. After the 20th gestational week, prednisone is recommended for 1-2 weeks before the initiation of chemotherapy. The preferred chemotherapeutic agents includecytarabine, cyclophosphamide, anthracyclines, vincristine and steroids Methotrexate is recommended only in the third trimester.
Chronic myeloid leukemia	Philadelphia chromosome t (9:22), leading to the excessive production of white blood cells in the bone marrow	Exposure to ionizing radiation, advanced age and male sex	Leukapheresis, chemotherapy, INF-α and tyrosine kinase inhibitors
Chronic lymphocytic leukemia	Clonal expansion of $CD5^+$ $CD23^+$ B cells in blood, marrow and lymphoid tissues	Family history, autoimmune diseases, exposure to pesticides, and insecticides, and hepatitis C infection	There are no leading directions due to limited data
Hairy cell leukemia	Expression of a range of B-cell antigens (surface Ig, CD19, CD20 and CD22); expression ofa single light-chain type and clonal rearrangement of Ig	Age, sex (more common in men than in women) and ethnicity (more often found in the family history of white patients)	INF-α, cladribine and rituximab

ALL, acute lymphoblastic leukemia; BCR, B-cell receptor; INF-α, interferon-α; Ig, immunoglobulin.

chemotherapy is proposed, mainly vinblastine, which is less harmful than other chemotherapeutic agents. Adriamycin, bleomycin, vinblastine and dacarbazine are also suggested in markedly aggressive lymphomas, while radiotherapy is postponed until after birth due to the risk of teratogenesis and cancer development in childhood (47).

Therapeutic approach for HL in the second and third trimesters of pregnancy. Management of HL in the second and third trimesters is easier due to a wide range of therapeutic options. If asymptomatic HL is diagnosed during the second half of the pregnancy, then therapy is not provided, but treatment is suggested after the completion of childbirth. If immediate treatment is crucial, then there are chemotherapeutic schemes such as ABVD. Some possible toxic effects of this chemotherapeutic scheme are low bodyweight embryos, limited endometrial development, birth of a dead embryo, mental retardation and learning difficulties during childhood. In addition to these possible effects, previous research has shown that embryo exposure to these agents is limited. Radiation is not suggested during pregnancy due to its long-term impact on embryos. If radiation is necessary, it is used after the first trimester and the abdomen is covered to prevent exposure to radiation (48). The timing of childbirth is a shared decision of gynecologists, hematologists, oncologists and patients. Whenever it is possible and permitted by the health of the mother and the fetus, the pregnancy is allowed to be completed. If this is impossible, the fetus should be born after the 34th week of gestation. Childbirth by cesarean section is not necessary, except if there are other obstetrical reasons. A previous study has shown that fertility is possibly affected after chemotherapy or radiotherapy. There are chemotherapeutic schemes that appear to be less harmful for infertility such as ABVD, and others that are more harmful such as BEACOPP. Additionally, the larger the dose of medications is, the greater the possibility of infertility. In addition, it is not possible to estimate in detail the effect of these medications or radiotherapy on the fertility of women. Chemotherapy can lead to premature ovarian insufficiency and premature menopause. Specific medications such as procarbazine and cyclophosphamide result in 5-25% premature ovarian insufficiency mainly in women aged <30 years. Doxorubicin, bleomycin, vincristine and dacarbazine pose a smaller risk of premature ovarian insufficiency (49). For this reason, cryopreservation of ovaries is essential before the beginning of therapy. Another promising method is the cryopreservation of ovarian tissue, which has been used in a few cases of women with HL who desire future pregnancy. Planning for a possible pregnancy is recommended 2 years after the completion of therapy, since patients with HL can relapse in the first decade (49).

Non-HL (NHL). NHL is a hematological malignancy of either B- or T-cell origin. The incidence of this disease increases with age and is usually diagnosed in patients >60 years of age. NHL is classified into two groups, aggressive and indolent, which have different prognoses. The most aggressive type of NHL is Burkitt lymphoma, which is also one of the most rapidly developing types of tumor (50). Aggressive lymphoma cells rapidly divide in the body, and, if left untreated, they can result in mortality within 6 months. Patients that are diagnosed in the early stages of aggressive disease, have more possibilities to be cured and less possibilities of relapse.

Pathophysiology of NHL. Chromosome translocation causes NHL to develop in B, T or natural killer cells. The most prevalent chromosomal aberration in NHL is the t (14;18) translocation. Oncogenes are activated and tumor suppressor genes are inactivated due to translocations (51). Biological markers play a crucial role in the clinical management of NHL by supporting morphologic diagnosis, staging, prognostic assessment and monitoring of MRD. Serological markers such as β2-microglobulin (β2-M), lactate dehydrogenase (LDH) and cancer antigen 125 reflect tumor load, proliferative activity and invasive potential, respectively. LDH and β2-M are important prognostic parameters included in widely used staging systems. Immunophenotypic analysis helps to identify lineage (B or T cells), maturation level, cell proliferation and clonality, thus providing valuable insights into the disease biology and guiding treatment decisions (51,52).

Risk factors of NHL. Risk factors involved in the disease are genetic predisposition, Epstein-Barr infection, immunosuppression, human immunodeficiency virus, *Helicobacter pylori* or hepatitis C infections, obesity, exposure to chemical substances (benzene, ethylene oxide and formaldehyde) and autoimmune diseases, in addition to silicone implants in the case of T-cell anaplastic lymphoma (52).

General therapeutic approach for NHL. The therapeutic approach for NHL includes the use of immunochemotherapy, radiotherapy, targeted therapies and transplantation of hemopoietic progenitor cells, as well as the recent use of CAR T-cell technology. The most known widely used chemotherapeutic regimen is rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) (53).

NHL in pregnancy. NHL is rare in pregnancy, and it affects extranodular locations such as the breasts, ovaries and vagina. The most frequent subtype of NHL in pregnancy is diffuse B-cell lymphoma (54).

Clinical presentation of NHL in pregnancy. The symptoms of NHL are not different from those that appear in non-pregnant women. Regarding these, painless lymphadenopathy is often manifested, while the presence of systemic symptoms (known as B symptoms), such as fever, abundant night sweats and loss of >10% body weight over 6 months is frequent (54).

Diagnosis of NHL in pregnancy. The diagnosis of NHL in pregnancy should always include history, physical examination and blood tests. Bone marrow biopsy and/or cerebrospinal fluid evaluations establish the final diagnosis of the disease (55).

Therapeutic approach for NHL in pregnancy. The decision regarding therapy in pregnancy is dependent on several factors, including the type of lymphoma, week of the pregnancy and patient's preference. Asymptomatic and non-aggressive lymphomas can be managed with supervision, while aggressive lymphomas require systematic treatment (55). As for the treatment, combined chemotherapy can be used with certain

safety in the second and third trimesters, but is contraindicated during the first trimester. Regarding non-aggressive NHLs (nodular and lymphocytic), treatment can be delayed until the appearance of symptoms. If the patient remains asymptomatic, it is suggested to start the treatment after childbirth. If it is symptomatic and the treatment in the first trimester is necessary, rituximab is exclusively recommended. The use of rituximab in pregnancy is associated with abortions in the first trimester in a percentage of 21%, with neonatal prematurity in a percentage of 24%, and with neutropenia, thrombocytopenia and a reduced number of B cells in the neonate after birth. The additional therapeutic choice in the second and third trimesters for non-aggressive lymphomas is cyclophosphamide, vincristine and prednisolone (CVP) (56). The treatment of non-aggressive lymphomas can be initiated after the first trimester. Aggressive lymphomas are diagnosed often during pregnancy, and must be treated immediately and in combination with other agents. When the diagnosis is made early in the first trimester, termination of pregnancy is suggested. If the diagnosis is made at the end of the first trimester, CHOP is suggested in the second trimester, while the combination of rituximab with CHOP is considered the most effective one in pregnancy. Concerning the most aggressive NHLs, termination of pregnancy in the first trimester is advised (56,57). According to limited bibliographic data, methotrexate has been used in the second and third trimesters, and it is not considered to have teratogenic effects but can cause myelosuppression of the embryo (56,57). Treatment for NHL can have adverse effects on fertility, mainly the combination of chemotherapeutic agents and radiotherapy (58). A temporary period of infertility may occur subsequent to treatment of the disease, while irreversible infertility rarely occurs.

10. Multiple myeloma

MM. MM is defined as a multifocal neoplasm characterized by the expansion of clonal plasma cells in the bone marrow, soft tissues and bones. MM is characterized by the presence of monoclonal proteins in serum and urine (59). In the majority of cases, asymptomatic myeloma exists prior to the development of MM (60). The production of monoclonal paraproteins results in their accumulation in several organs (kidney, heart, liver and peripheral neurons) and in the manifestation of symptoms such as amyloidosis or hyperviscosity syndrome.

Pathophysiology of MM. Monoclonal plasma cells in myeloma proliferate and produce excessive M protein levels, abnormal light chain proteins and cytokines that stimulate osteoclasts and suppress osteoblasts, and angiogenesis factors that lead to new blood vessel formation. Therefore, the overproduction of M protein level can cause hyperviscosity and light chain protein-associated end organ damage, especially in the kidneys, as well as bone lesions, osteoporosis and hypercalcemia (Fig. 2). Bone marrow invasion can result in anemia and recurrent infections (61).

Risk factors of MM. Age >55 years old, male sex, black ethnicity and history of monoclonal gammopathy of undetermined significance are associated with the development of MM (62).

General therapeutic approach for MM. The treatment of MM depends on the age of the patient. Induction chemotherapy with bortezomib and lenalidomide-dexamethasone is used in patients <65 years old and is followed by stem cell transplantation (63). In patients >65 years old that cannot tolerate stem cell transplantation, chemotherapy is recommended. Combination of daratumumab (an anti-CD38 monoclonal antibody) with either bortezomib or lenalidomide can possibly offer an overall improved life expectancy. On average, the 5-year survival rate is 35-50% (64).

MM in pregnancy. The coexistence of MM and pregnancy is rare, since the disease affects mainly older patients, and is usually found in the third trimester (65).

Clinical presentation of MM in pregnancy. Hypercalcemia, renal impairment, anemia and bone osteolysis require immediate treatment (66), as well as patients with ≥1 focus lesion on MRI imaging (67) or infiltration by plasma cells in the bone marrow. The symptoms that are more often reported during diagnosis are lower back pain, pale skin, anemia, weight loss and fatigue. MM usually leads to frequent infections and osteolytic lesions resulting in bone fractures, and can cause severe disability and permanent neurological impairment (65).

Diagnosis of MM in pregnancy. Suspicion of the disease arises from laboratory pathological tests, such as complete blood count, elevated erythrocyte sedimentation rate, and measurement of calcium, albumin, lactic dehydrogenase, urea and creatinine in blood. The results reflect bone marrow and renal insufficiency, and bone lesions attributed to MM, while measurement of β2-M and serum albumin are recommended to determine the stage of the disease. Increased β2-M levels determine the prognosis, while the IgG or IgA levels reflect the tumor burden (68). Serum and urine protein electrophoresis should not be omitted. Urine tests measure red blood cells, glucose and proteins; however, the existence of MM is indicated by a 24-h urine collection for the detection of light chains of proteins (Bence-Jones proteins). Additional diagnostic techniques include CT, MRI, PET scans and X-rays. A bone marrow biopsy is used to establish the final diagnosis (69).

Therapeutic approach for MM in pregnancy. Regarding the treatment for MM, glucocorticoids until childbirth are suggested. Chemotherapy in the first trimester is considered dangerous for the fetus, while its administration during the second and third trimesters is not considered to be harmful. In the advanced cases of disease, in which chemotherapy is necessary in the first trimester, termination of pregnancy is suggested. Thalidomide, lenalidomide and pomalidomide are medications that are used in the treatment of MM, but their administration during pregnancy and during puerperium is strictly contraindicated. The consequences of bortezomib in embryo development are not clear because there are no clinical studies on it. Cyclophosphamide is used because it inhibits the development and multiplication of malignant cells (70). Dexamethasone and prednisone are considered safe in pregnancy. Bisphosphonates prevent bone fractures and are considered safe in pregnancy. The most frequently used bisphosphonates are pamidronate and zoledronic acid. It is

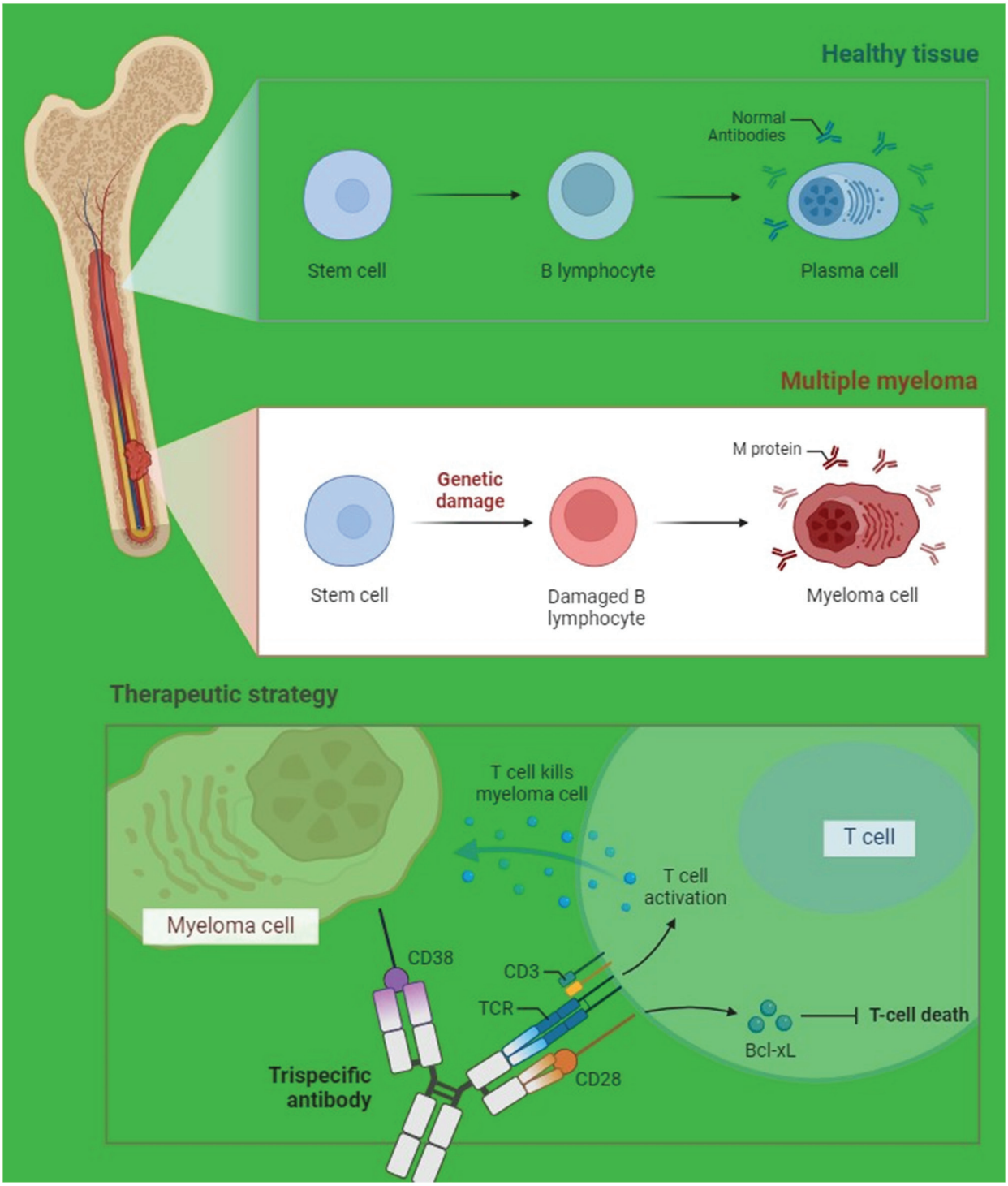

Figure 2. Representation of healthy plasma cells, damaged plasma cells with M protein and therapeutic approaches in MM. The healthy plasma cell image is a depiction of a normal, functioning plasma cell, responsible for producing antibodies to fight infections. The cell exhibits regular morphology and produces a diverse range of antibodies to maintain the immune system function. For representing a damaged plasma cell with M protein, the illustration of a plasma cell afflicted by a cancer of plasma cells is shown. The cell displays aberrant morphology and produces excessive levels of monoclonal antibodies known as M proteins. These abnormal proteins can interfere with normal immune functions, and cause complications such as kidney damage and bone lesions. Regarding therapeutic approaches for MM, various treatment modalities for MM are proposed, including chemotherapy, immunomodulatory drugs, proteasome inhibitors, stem cell transplantation and targeted therapies. These interventions aim to eliminate malignant plasma cells, reduce M protein levels and alleviate symptoms associated with the disease, ultimately improving the outcome and quality of life of patients. MM, multiple myeloma; BcL-xL, B-cell lymphoma-extra large.

still unknown if pregnancy deteriorates or not as the disease progresses (71). Fertility is reduced in women affected by MM who are treated with chemotherapy. One approach that is used for the maintenance of fertility in women affected by MM is the cryopreservation of embryos before chemotherapy, which can be implanted in the uterus after recovery from the disease (72). Pathophysiology, risk factors and treatment of HL, non-HL and MM are summarized in Table III.

Table III. Pathophysiology, risk factors and treatment of HL, non-HL and MM.

Types	Pathophysiology	Risk factors	Treatment
HL	Large cells known as Reed-Sternberg cells are a hallmark of HL, while other aberrant cell types may also be present	Male sex, age (15-40 and >55 years), positive family history of HL, history of infectious mononucleosis, immunosuppression (including HIV), use of growth hormone and exposure to exotoxins	In case of aggressive lymphomas, termination of pregnancy is suggested, while in the second and third trimesters of pregnancy, adriamycin, bleomycin, vinblastine and dacarbazine are recommended
Non-HL	Chromosome translocation causes non-HL to develop in B, T or natural killer cells. The most prevalent chromosomal aberration innon-HL is the t (14;18) translocation	Genetic predisposing, Epstein-Barr infection, immunosuppression (iatrogenic, hereditary or HIV-related), HIV infection, *Helicobacter pylori* or hepatitis C infections, obesity, exposure to chemical substances, autoimmune diseases and silicone implants (for T-cell anaplastic lymphoma)	Asymptomatic and non-aggressive lymphomas, supervision; aggressive lymphomas, systematic treatment. Combined chemotherapy can be used with relative safety in the second and third trimesters, but is contraindicated during the first trimester
MM	Monoclonal plasma cells proliferate and produce excessive M protein levels, abnormal light chain proteins and cytokines that stimulate osteoclasts and suppress osteoblasts, and angiogenesis factors that lead to new blood vessel formation	Advanced age (>55 years), sex (more common in males), ethnicity (double risk in black vs. Caucasian men) and history of monoclonal gammopathy of undetermined significance	Glucocorticoids until childbirth are suggested; chemotherapy in the first trimester is dangerous for the fetus, while chemotherapy during the second and third trimesters is not considered to be harmful

HL, Hodgkin lymphoma; MM, multiple myeloma; HIV, human immunodeficiency virus.

11. AML cases vs. bone marrow metastatic cancer

Exploring clinical treatment strategies and differential diagnosis in typical AML cases vs. bone marrow metastatic cancer. There is limited literature addressing the differences in treatment approaches between cases of leukemia and bone marrow metastases during pregnancy. However, data regarding gastric cancer metastasizing to the bone marrow are available. Performing a bone marrow biopsy for histopathological diagnosis is the most reliable method for distinguishing between these two clinical entities if the primary cancer has not been identified. Although it is beyond the scope of the present review, it remains important to differentiate between general bone marrow metastasis and disseminated carcinomatosis of the bone marrow (DCBM). In typical bone metastasis, the metastatic pattern manifests as a nodular pattern, whereas in DCBM, it presents as diffuse infiltration, leading to hematological disorders such as disseminated intravascular coagulation, leukoerythroblastosis and microangiopathic hemolytic anemia. DCBM arises from the metastasis of solid tumors, with ~90% of cases originating from gastric cancer (73-75).

The management of such patients poses significant challenges. It is advised to consider termination of pregnancy before 22 weeks of gestation and early delivery after 28 weeks of gestation when initiating treatment. However, the recommended treatment approach between 22 and 28 weeks of gestation is subject to debate. Immediate interventions such as systemic chemotherapy are beneficial for patients, although there is a risk of adverse effects on the fetus (74,75).

Administration of chemotherapy during the first trimester carries an elevated risk of congenital malformations. Unfavorable experiences of chemotherapy in the first trimester resulted in the recommendation for therapeutic abortion; in particular, the association of cytarabine and 6-thioguanine with congenital abnormalities led to the recommendation that both of these drugs should be avoided during this time period. Regimen-induced toxicity during the first trimester is well accepted, but as not all fetuses are adversely affected, there may be a genetic predisposition to teratogenesis. Thus, when acute leukemia is diagnosed in the first trimester, termination of pregnancy is strongly recommended, followed by the initiation of induction therapy. Conversely, if leukemia is diagnosed later in pregnancy, conventional management strategies akin to those in non-pregnant individuals can be employed, typically obviating the need for pregnancy termination. The risk of fetal malformation is generally acknowledged to decrease as the pregnancy progresses. Exposure to chemotherapy

after the first trimester is associated with a higher incidence of intrauterine growth retardation, which is also influenced by maternal nutritional status throughout pregnancy, as well as preterm delivery and fetal mortality. However, there is no observed increase in the occurrence of congenital abnormalities, and specifically, no documented increase in childhood malignancy or adverse neurological development, despite ongoing neurological development throughout gestation. Treatment during the third trimester typically yields the fewest complications; however, the timing of chemotherapy must be meticulously planned to avoid inducing pancytopenia immediately prior to delivery. Patients diagnosed with CML during pregnancy can often be managed with leukapheresis, chemotherapy (hydroxycarbamide), IFN-α and imatinib. Those with established CML and a sustained complete molecular response prior to conception may be monitored without treatment throughout the pregnancy. In the rare occurrence of CLL during pregnancy, treatment can typically be postponed until after delivery (76,77).

12. Future perspectives and conclusions

Future perspectives. Van Calsteren *et al* (78) explored the transplacental transmission of various chemotherapeutic agents from mother to fetus using both mouse and baboon models. The baboon model is considered a pertinent animal model due to its close phylogenetic resemblance to humans in terms of embryological development, reproductive physiology, placental structure and function, as well as drug metabolism. In the baboon model, notable discrepancies were observed in fetal plasma concentrations for each chemotherapeutic drug. Anthracyclines (doxorubicin and epirubicin) and taxanes (paclitaxel) exhibited limited transplacental transfer rates (<10 and <2%, respectively). Conversely, carboplatin showed the highest fetal compartment concentration (>55%), indicative of its considerable transplacental passage (78).

Building upon the aforementioned findings, future perspectives could include: i) Further investigation on transplacental transfer by conducting studies to explore the transplacental transfer of chemotherapeutic drugs in different animal models, including non-human primates, to validate and expand upon the observed patterns; ii) mechanistic understanding by delving deeper into the mechanisms underlying the varying transplacental transfer rates of different chemotherapeutic agents, including factors such as drug properties, placental transport mechanisms and fetal metabolism; iii) clinical implications by translating these findings into clinical practice by informing treatment strategies for pregnant patients with cancer, which may involve refining dosing regimens, selecting drugs with lower fetal exposure or developing novel approaches to minimize fetal harm while ensuring maternal therapeutic efficacy; iv) pharmacokinetic modeling by developing pharmacokinetic models to predict the transplacental transfer of chemotherapeutic agents in pregnant individuals, thus aiding clinicians in optimizing treatment regimens and monitoring fetal exposure; and v) long-term follow-up by conducting long-term follow-up studies to assess the impact of prenatal exposure to chemotherapeutic agents on fetal development, birth outcomes and childhood health, thus providing valuable insights into the safety profile of these treatments during pregnancy.

Overall, future research should aim to enhance the current understanding of the complex interplay between maternal cancer treatment, placental physiology and fetal development, ultimately improving the care and outcomes of pregnant individuals with cancer.

Conclusions. The incidence of leukemias in pregnancy is low, with acute leukemia and mainly AML predominance. For acute leukemias, immediate treatment after diagnosis is necessary. Therapeutic approach and management should be personalized according to the trimester of pregnancy. More specifically, termination of pregnancy is recommended in the first trimester, while chemotherapeutic schemes and labor induction are preferred after the 32nd gestational week.

Management of pregnant women with chronic leukemias differs from management of those with acute ones. Asymptomatic pregnant women are not treated unless symptoms appear. Various therapeutic schemes have been used as monotherapy or combined therapy. Leukemias do not inhibit a future pregnancy. Regarding the estimated time of childbearing, women receiving or about to receive medication for leukemias, family planning and counseling from a specialized medical team is recommended.

The clinical picture and diagnosis of lymphomas are not different in pregnant women compared to the rest of the population. Most lymphomas are treatable during pregnancy. One pregnancy can end up full-term when the mother's and embryo's health allows it. In asymptomatic lymphomas, follow-up of the disease is recommended, while in symptomatic and/or aggressive lymphomas, immediate therapy is suggested during the second and third trimesters of pregnancy. In symptomatic lymphomas, during the first trimester, administration of chemotherapeutic agents or monoclonal antibodies is necessary. For women who manifest the disease at the beginning of the first trimester, termination of pregnancy is recommended. Temporary infertility of patients is affected by using chemotherapeutics because they lead to premature ovarian insufficiency. If the disease is manifested mainly during the third trimester of pregnancy with atypical symptoms, therapy is based on glucocorticoids. In women affected by MM, cryopreservation of egg cells or embryos is suggested before the beginning of chemotherapy.

The present review emphasizes the importance of prompt diagnosis and tailored management of leukemias and lymphomas during pregnancy. Immediate treatment is crucial for acute leukemias, with consideration given to trimester-specific approaches and potential termination in the first trimester. Chronic leukemias may not require immediate intervention unless symptoms arise. Family planning and counseling are essential for women receiving or planning to receive leukemia treatment. Lymphomas may require immediate therapy depending on their symptoms and aggressiveness, while fertility preservation measures are recommended before chemotherapy for MM. Overall, the current review underscores the need for personalized care and timely intervention to optimize outcomes for both the mother and fetus.

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Authors' contributions

AGG participated in the review process and prepared the manuscript. MNG collected data and relevant literature. EO contributed to manuscript corrections, and collected data and relevant literature. KN, AB, SK, NK, SA and TN collected data and literature. ES, GI, CD, NG and NN corrected and modified the manuscript. PT was responsible for the study protocol and contributed to the study design, participated in the review process, prepared the manuscript and made substantive intellectual contributions to the published study. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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