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INDICATORS OF FEMALE INFERTILITY IN TRANSFUSION-DEPENDENT PATIENTS WITH BETA-THALASSEMIA MAJOR: A SYSTEMATIC REVIEW

Sausen Kareem Suadi[1*], Dina Ali Khalil[1], Azhar Ibraheem Alwan[2]

[1] Al-Diwaniyah Teaching Hospital for Maternity and Children, Al-Diwaniyah, Iraq
[2] Ramadi Teaching Hospital for Maternity and Children, Ramadi, Iraq

Corresponding email: bocean68@yahoo.com DOI: 10.5281/zenodo.24208827

ABSTRACT

Background: Women with transfusion-dependent beta-thalassemia major (BTM) now commonly reach reproductive age, yet infertility remains a major complication. **Objectives:** This systematic review evaluated clinical, endocrine, ovarian reserve, and imaging indicators of female infertility in this population. **Methods:** Following PRISMA 2020 guidance, PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library were searched from 1990 to January 2026, and the findings were synthesized narratively because of heterogeneity. **Results:** Twenty-five studies were included (19 original studies and six reviews or guidelines). Hypogonadotropic hypogonadism was the dominant endocrine abnormality and presented mainly as primary or secondary amenorrhea. Pituitary iron overload and volume loss on magnetic resonance imaging (MRI) were the indicators most consistently associated with hypogonadism. Anti-Müllerian hormone and antral follicle count were lower than in age-matched controls in most studies, although ovarian reserve appeared largely preserved in younger women. Serum ferritin was inconsistently associated with reproductive dysfunction. Pregnancies after ovulation induction and in vitro fertilization were reported, with preserved oocyte quality despite reduced ovarian reserve. **Conclusions:** Female infertility in BTM is driven mainly by iron-related pituitary injury, with a variable contribution from direct ovarian damage. Assessment should therefore combine menstrual history, gonadotropins, ovarian reserve markers, and pituitary MRI, and the results should guide early intensification of chelation and fertility counseling.

Keywords: Beta-thalassemia major; Female infertility; Hypogonadotropic hypogonadism; Iron overload; Ovarian reserve

1. INTRODUCTION

Beta-thalassemia major (BTM) is a hereditary hemoglobinopathy characterized by ineffective erythropoiesis and severe anemia, necessitating lifelong regular red blood cell transfusions (Farmakis et al., 2022; Taher et al., 2018). The disorder is particularly common in the Mediterranean region, the Middle East, and South-East Asia, where it places a sustained burden on affected families and health services (Taher et al., 2018; Tsilionis et al., 2024). With the advent of standardized transfusion protocols and more effective iron chelation therapy, survival into adulthood has improved substantially, shifting the clinical focus toward long-term morbidity and quality-

of-life outcomes, including reproductive health (Borgna-Pignatti and Gamberini, 2011; Farmakis et al., 2022; Taher et al., 2018).

Chronic transfusion therapy leads to progressive iron overload, with preferential deposition in endocrine organs such as the pituitary gland, pancreas, thyroid, and gonads (Borgna-Pignatti and Gamberini, 2011; Cappellini et al., 2014; Farmakis et al., 2022). Because the body has no active pathway for iron excretion, transfused iron accumulates; once transferrin becomes saturated, non-transferrin-bound and labile plasma iron enter tissues and generate reactive oxygen species (Roussou et al., 2013; Singer et al., 2011). As a result, endocrine dysfunction represents one of the most prevalent and clinically significant late complications of transfusion-dependent thalassemia (TDT) (Belhoul et al., 2012; Borgna-Pignatti & Gamberini, 2011; Farmakis et al., 2022; Taher and Saliba, 2017). Among these, disorders of the hypothalamic-pituitary-gonadal (HPG) axis are particularly common and have a major impact on female fertility.

Hypogonadotropic hypogonadism (HH), caused primarily by iron deposition in the anterior pituitary, is reported in approximately 25-90% of patients with TDT, depending on age, treatment era, and chelation (Belhoul et al., 2012; Mahwi et al., 2023; Poggi et al., 2016; Tsilionis et al., 2024). Clinically, HH manifests as delayed puberty, arrested pubertal development, primary or secondary amenorrhea, and infertility (Borgna-Pignatti and Gamberini, 2011; De Sanctis et al., 2019). Importantly, pituitary dysfunction may be subclinical for years before overt reproductive failure becomes apparent, emphasizing the need for sensitive early indicators of pituitary iron toxicity (Christoforidis et al., 2007; Noetzli et al., 2012; Singer et al., 2021).

In parallel with central mechanisms, accumulating evidence suggests that iron overload may also exert direct gonadotoxic effects on the ovaries. Experimental and clinical data implicate iron-mediated oxidative stress in granulosa cell dysfunction, mitochondrial injury, impaired steroidogenesis, and accelerated follicular atresia (Roussou et al., 2013; Tsilionis et al., 2024). These processes raise concern for diminished ovarian reserve and, in some patients, primary ovarian insufficiency, even in the absence of overt pituitary failure (Chang et al., 2011; Matter et al., 2026; Talaulikar et al., 2019; Uysal et al., 2017). Consequently, female infertility in BTM is increasingly recognized as a multifactorial condition involving both central (pituitary) and peripheral (ovarian) components (Figure 1).

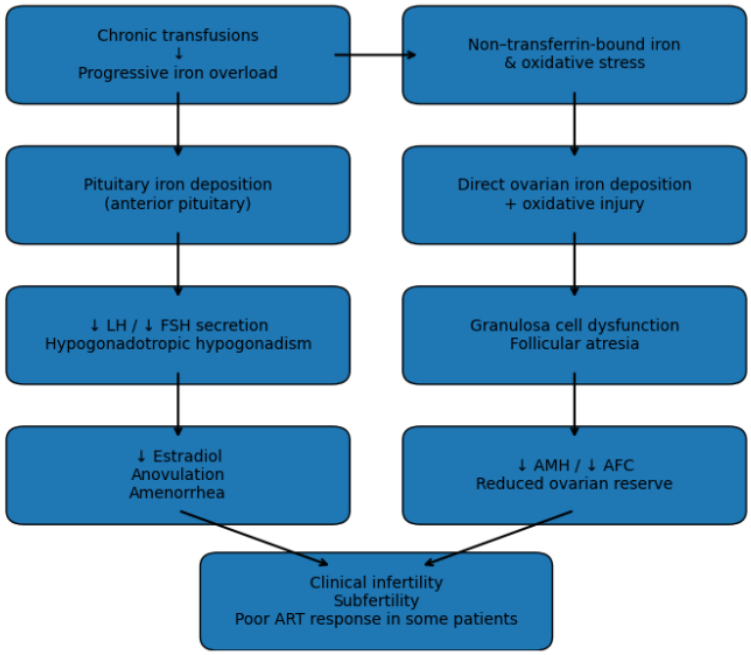

Figure 1. Proposed pathways of iron-related reproductive damage in women with transfusion-dependent beta-thalassemia major. The left arm shows central (pituitary) injury leading to hypogonadotropic hypogonadism; the right arm shows direct ovarian injury leading to reduced ovarian reserve. LH, luteinizing hormone; FSH, follicle-stimulating hormone; AMH, anti-Müllerian hormone; AFC, antral follicle count; ART, assisted reproductive technology.

The clinical landscape of fertility in BTM has evolved over the past two decades. Whereas spontaneous fertility was historically uncommon, more recent cohorts report increasing numbers of spontaneous conceptions and successful assisted reproductive technology (ART) outcomes, particularly among women who received early and intensive chelation therapy (Mensi et al., 2019; Origa et al., 2010). This improvement underscores the need for accurate, reproducible, and clinically practical indicators to stratify fertility risk, guide counseling, and inform fertility preservation strategies such as oocyte or ovarian tissue cryopreservation (Farmakis et al., 2022; Tsilionis et al., 2024).

Traditional assessment of reproductive function relied primarily on menstrual history and serum gonadotropins. However, newer tools, including anti-Müllerian hormone (AMH), antral follicle count (AFC), and magnetic resonance imaging (MRI)-based iron quantification (including pituitary R2 and T2* and cardiac T2*), have expanded the ability to detect subclinical reproductive dysfunction (Chang et al., 2011; Christoforidis et al., 2007; Noetzli et al., 2012; Singer et al., 2011; Singer et al., 2021; Talaulikar et al., 2019).

Despite these advances, the evidence remains fragmented. Previous reviews have addressed either the mechanisms of iron-induced gonadal injury (Roussou et al., 2013) or ovarian reserve and endocrine complications (Tsilionis et al., 2024), while international guidelines recommend regular endocrine surveillance without specifying which indicators best predict infertility (Farmakis et al., 2022). The available studies also disagree on key points: some report markedly reduced AMH and AFC in women with BTM (Chang et al., 2011; Özcan et al., 2023; Uysal et al., 2017), whereas others describe a largely preserved ovarian reserve in younger women despite central hypogonadism (Singer et al., 2011). In addition, the

proposed pituitary MRI thresholds were derived from relatively small cohorts and have not been standardized (Christoforidis et al., 2007; Noetzli et al., 2012; Singer et al., 2021). To our knowledge, no systematic review has evaluated clinical, endocrine, ovarian reserve, and imaging indicators together, compared their predictive value, and examined why studies reach different conclusions. This gap must be addressed before these markers can be combined into a unified clinical approach.

Therefore, this systematic review synthesizes the evidence from 25 studies, including international guidelines, on clinical, endocrine, ovarian reserve, and imaging indicators of female infertility in transfusion-dependent BTM. We sought to (1) identify the most reliable indicators of infertility risk; (2) clarify the relative contributions of pituitary versus ovarian pathology; and (3) propose a pragmatic indicator framework to support early detection, fertility counseling, and individualized reproductive care in this growing population (Borgna-Pignatti & Gamberini, 2011; Farmakis et al., 2022; Taher and Saliba, 2017).

2. MATERIALS AND METHODS

2.1 Search strategy and data sources

A structured literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library for studies published between 1990 and January 2026, in accordance with PRISMA recommendations (Page et al., 2021). Search terms included combinations of: "beta-thalassemia major" or "transfusion-dependent thalassemia" and "female fertility" or "amenorrhea" or "hypogonadism" or "anti-Müllerian hormone" or "antral follicle count" or "pituitary MRI" or "T2*". Citation chaining from key reviews and international guidelines was also performed (Borgna-Pignatti & Gamberini, 2011; Farmakis et al., 2022; Taher and Saliba, 2017).

2.2 Eligibility criteria

Studies were eligible if they (i) included female patients with transfusion-dependent beta-thalassemia major (or mixed cohorts with extractable female BTM data); (ii) reported reproductive, endocrine, ovarian reserve, or fertility outcomes; and (iii) were observational studies, interventional cohorts, or guideline/consensus documents. Case reports with <5 patients and studies limited to thalassemia intermedia or other non-transfusion-dependent thalassemias were excluded.

2.3 Outcomes and indicators of interest

Predefined indicators included (i) clinical outcomes (primary/secondary amenorrhea, delayed or arrested puberty, menstrual regularity); (ii) biochemical markers (LH, FSH, estradiol, AMH, inhibin B, prolactin); (iii) imaging markers (pituitary R2 and T2*, pituitary volume or height, cardiac T2*, liver iron concentration); and (iv) fertility outcomes (spontaneous conception, ovulation induction, assisted reproductive technology, pregnancy/live birth) (Broer et al., 2014; Farmakis et al., 2022; La Marca et al., 2010; Tsilionis et al., 2024).

2.4 Study selection and synthesis

Titles and abstracts were screened, followed by full-text review. Disagreements were resolved by consensus. Due to heterogeneity of study designs and outcome reporting, a quantitative meta-analysis was not performed; instead, results were synthesized narratively with emphasis on consistency of indicators and clinical applicability, in line with prior thalassemia and endocrine reviews (Borgna-Pignatti and Gamberini, 2011; Roussou et al., 2013; Tsilionis et al., 2024). For presentation, indicators were

grouped in a fixed sequence, clinical and menstrual, endocrine, ovarian reserve, and imaging and iron burden, followed by fertility outcomes, and this sequence is used throughout the Results and Discussion. Study selection is summarized in the PRISMA flow diagram (Figure 2), consistent with PRISMA 2020 guidance (Page et al., 2021).

3. RESULTS

3.1 Study selection

The database search identified 300 records, and a further 25 were identified from other sources. After removal of duplicates, 247 records were screened, 74 full-text articles were assessed for eligibility, and 49 were excluded, leaving 25 studies for the qualitative synthesis (Figure 2). These comprised 19 original research studies (prospective and retrospective cohorts, case-control studies, and cross-sectional clinical and imaging studies) and six narrative reviews or international guidelines (Table 1). The included studies spanned pediatric to adult populations and reflected a range of chelation eras and iron burden profiles.

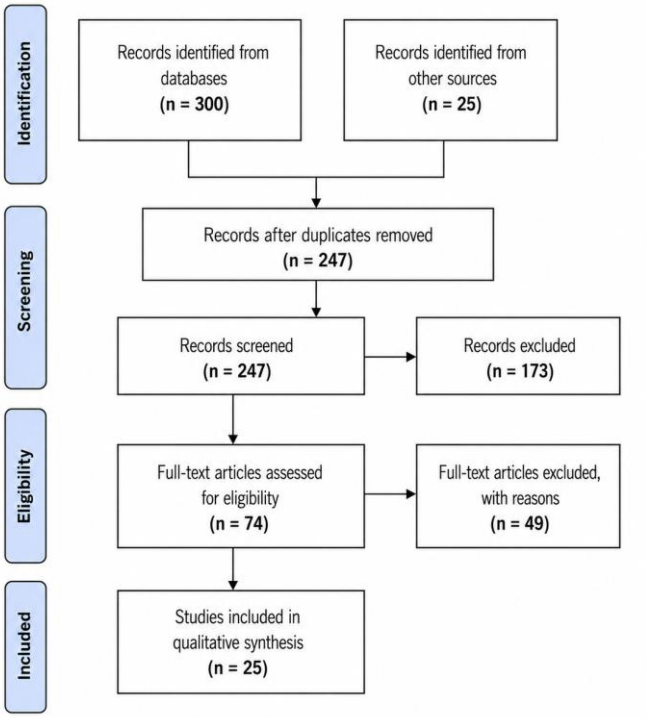

Figure 2. PRISMA 2020 flow diagram of study identification, screening, eligibility assessment, and inclusion (searches completed in January 2026).

3.2 Study characteristics

The main characteristics of the included studies are summarized in Table 1, in which original research studies are listed separately from reviews and guidelines. Sample sizes of the original studies ranged from 17 women in a ten-year longitudinal cohort (Talaulikar et al., 2019) to 957 patients in a national multicentre imaging network (Gamberini et al., 2011); ten studies enrolled women only, and the remainder were mixed-sex cohorts with extractable female data. Across studies, hypogonadotropic hypogonadism, menstrual abnormalities, and ovarian reserve impairment were consistently reported, with pituitary MRI parameters emerging as the most reproducible predictors of hypogonadism (Christoforidis et al., 2007; Noetzli et al., 2012; Singer et al., 2021).

Table 1. Characteristics of the 25 studies included in the systematic review

Author (year)	Country	Study design	n	Key outcomes
A. Original research studies (n = 19)				
Talaulikar et al. (2019)	UK	Longitudinal cohort (10 years) with controls	17 F	AMH and AFC lower than in 52 age-matched controls, with progressive decline
Singer et al. (2021)	USA	Cross-sectional imaging	53 (27 F)	Pituitary iron and volume loss independently linked to hypogonadism; cardiac T2* <20 ms and LIC >10 mg/g associated with pituitary iron
Chang et al. (2011)	Taiwan	Case-control	29 F	AMH, LH, and estradiol lower than controls; AMH inversely related to ferritin
Matter et al. (2026)	Egypt	Case-control	50 F	Ovarian insufficiency in 40%; pituitary R2* the strongest independent predictor
Poggi et al. (2016)	Italy	Retrospective longitudinal (5 years)	165	Hypogonadism in 65.5% at baseline; endocrine outcomes differed by chelator
Alkatawe et al. (2025)	Iraq	Case-control	90 F	Ferritin inversely correlated with FSH and estradiol; better chelation adherence linked to higher FSH and estradiol
Skordis et al. (2006)	Cyprus	Retrospective cohort	126	Higher transfusion requirement associated with hypogonadism
Origa et al. (2010)	Italy	Multicentre retrospective	46 F	58 pregnancies, 91% ending in live birth; 33 women conceived after gonadotropin-induced ovulation
Mensi et al. (2019)	Italy	Matched retrospective cohort (IVF)	21 F	Lower AMH and AFC than controls, but oocyte and embryo quality preserved
De Sanctis et al. (2019)	Italy	Retrospective cohort	42 F	Clinical phenotype and management of

Author (year)	Country	Study design	n	Key outcomes
				hypogonadism in female adolescents and young adults
Belhoul et al. (2012)	UAE	Cross-sectional	382	Hypogonadism in 25.9%; ferritin >2,500 µg/L associated with 2.75-fold higher odds
Gamberini et al. (2011)	Italy	Cross-sectional imaging (MIOT network)	957	Endocrine disease, including hypogonadism, associated with cardiac complications on MRI
Noetzli et al. (2012)	USA	Cross-sectional imaging	56	Pituitary R2 Z >5 and volume Z <-2.5 independently predicted hypogonadism
Gamberini et al. (2008)	Italy	Longitudinal cohort (1980-2007)	273	Incidence of endocrine complications declined with improved chelation
Mahwi et al. (2023)	Iraq	Cross-sectional	80 (53 F)	Hypogonadism in 68.8%, central in 96%; more frequent in women
Singer et al. (2011)	USA	Cross-sectional	26 F	Low AFC with mostly normal AMH; reserve declined after 30-35 years
Uysal et al. (2017)	Turkey	Case-control	43 F	AMH, AFC, and ovarian volume lower than 44 controls
Özcan et al. (2023)	Turkey	Prospective cohort (1 year)	41 F	AMH below age norms; lower in amenorrheic women
Christoforidis et al. (2007)	Greece	Cross-sectional imaging	30 (13 F)	Lower pituitary T2*-weighted signal in hypogonadal patients
B. Reviews and guidelines (n = 6)				
Tsilionis et al. (2024)	Greece	Narrative review	-	HH prevalence 40-91%; ovarian reserve frequently impaired
Roussou et al. (2013)	Greece	Narrative review	-	Iron and oxidative stress impair fertility
Farmakis et al. (2022)	International	Guideline (TIF)	-	Endocrine surveillance and fertility care recommended

Author (year)	Country	Study design	n	Key outcomes
Taher and Saliba (2017)	International	Review	-	Organs accumulate iron at different rates, so liver iron does not reflect endocrine iron
Berdoukas et al. (2011)	International	Review	-	Intensive chelation to prevent iron-related organ damage
Borgna-Pignatti and Gamberini (2011)	Italy	Review	-	Hypogonadism among the commonest complications of BTM

AFC, antral follicle count; AMH, anti-Müllerian hormone; BTM, beta-thalassemia major; F, female participants; FSH, follicle-stimulating hormone; HH, hypogonadotropic hypogonadism; IVF, in vitro fertilization; LH, luteinizing hormone; LIC, liver iron concentration; MIOT, Myocardial Iron Overload in Thalassemia; MRI, magnetic resonance imaging; n, number of patients with BTM (female number in parentheses for mixed-sex cohorts); TIF, Thalassaemia International Federation; UAE, United Arab Emirates. A dash (-) indicates not applicable.

3.3 Clinical and menstrual indicators

Primary and secondary amenorrhea, delayed puberty, and oligomenorrhea were highly prevalent across cohorts, reflecting both early and progressive pituitary dysfunction (De Sanctis et al., 2019; Mahwi et al., 2023; Özcan et al., 2023; Uysal et al., 2017). In the cohort of Uysal et al. (2017), 22 of 43 women were hypogonadotropic, eight with primary and 14 with secondary amenorrhea; 25 of 41 women (61%) studied by Özcan et al. (2023) were amenorrheic; and in an Iraqi cohort, 42 of 53 women (79%) were hypogonadal (Mahwi et al., 2023). Adolescent girls with TDT also reached menarche significantly later than controls (Matter et al., 2026). These clinical features correlated with biochemical HH and with pituitary MRI abnormalities, reinforcing their role as accessible frontline indicators of reproductive risk (Christoforidis et al., 2007; Noetzli et al., 2012; Singer et al., 2021) (Table 2).

Table 2. Clinical and menstrual indicators

Indicator	Reported findings	Clinical significance
Primary amenorrhea	8/43 women (19%)	Early-onset or severe HH
Secondary amenorrhea	14/43 (33%); overall amenorrhea 25/41 (61%)	Progressive pituitary failure
Hypogonadism in women	42/53 (79%); central in 96% of hypogonadal patients	Predominantly pituitary origin
Delayed menarche	Significantly later than controls	Early pituitary iron deposition
Amenorrhea with low AMH	AMH lower in amenorrheic than in cycling women	Combined central and ovarian involvement

Sources: Uysal et al. (2017); Özcan et al. (2023); Mahwi et al. (2023); Matter et al. (2026). AMH, anti-Müllerian hormone; HH, hypogonadotropic hypogonadism.

3.4 Endocrine (HPG axis) indicators

Across multiple cohorts, biochemical patterns consistent with hypogonadotropic hypogonadism (low or inappropriately normal LH and FSH with low estradiol) were the dominant endocrine phenotype (Chang et al., 2011; Mahwi et al., 2023; Uysal et al., 2017). In the cohort of Mahwi et al. (2023), hypogonadism was central in 53 of 55 affected patients (96%), and Chang et al. (2011) found lower LH and estradiol in women with TDT than in age-matched controls. Because low gonadotropin secretion masks the rise in FSH that normally accompanies follicle depletion, FSH alone could not reliably separate central from primary ovarian failure, which is why gonadotropins were interpreted together with markers of ovarian reserve (Matter et al., 2026; Singer et al., 2011) (Table 3).

3.5 Ovarian reserve indicators

AMH levels were significantly lower than controls in several studies, while others demonstrated relatively preserved AMH despite central hypogonadism, highlighting heterogeneity in ovarian involvement (Chang et al., 2011; Matter et al., 2026; Özcan et al., 2023; Singer et al., 2011; Talaulikar et al., 2019; Uysal et al., 2017). Uysal et al. (2017) found lower AMH, AFC, and ovarian volume in 43 women with BTM than in age-matched controls, and Özcan et al. (2023) reported a mean AMH of 2.7 ng/mL, significantly below the age-specific reference, with lower values in amenorrheic women. Talaulikar et al. (2019) observed lower AMH and AFC than in controls over ten years of follow-up, and women undergoing IVF had a median AFC of 4 compared with 11 in matched controls (Mensi et al., 2019). In contrast, Singer et al. (2011) found AMH mostly within the normal range in women younger than 30-35 years, despite low AFC. Inhibin B was rarely measured, and its value in this population remains uncertain.

Table 3. Hormonal and ovarian reserve indicators of infertility

Marker	Typical finding	Clinical significance
LH	Low	Pituitary damage
FSH	Low or inappropriately normal	Does not reliably separate central from ovarian failure
Estradiol	Low	Anovulation
AMH	Decreased vs age-matched controls; may be preserved in younger women	Reduced ovarian reserve
AFC (ultrasound)	Decreased vs controls (median 4 vs 11 in an IVF cohort)	Reduced reserve or lack of gonadotropin stimulation
Inhibin B	Rarely measured	Uncertain

Sources: Chang et al. (2011); Talaulikar et al. (2019); Singer et al. (2011); Uysal et al. (2017); Mensi et al. (2019); Mahwi et al. (2023); Özcan et al. (2023); Matter et al. (2026). AFC, antral follicle count; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; IVF, in vitro fertilization; LH, luteinizing hormone.

3.6 Imaging and iron burden indicators

Pituitary MRI measures (R2 and T2*, signal intensity ratios, and pituitary volume/height) were strongly associated with hypogonadism and infertility risk (Christoforidis et al., 2007; Matter et al., 2026; Noetzli et al., 2012; Singer et al., 2021). Noetzli et al. (2012) found that severe pituitary iron deposition (R2 Z-score >5) and volume loss (Z-score <-2.5) independently predicted hypogonadism, and Christoforidis et al. (2007) observed significantly lower pituitary T2*-weighted signal in hypogonadal patients. Cardiac T2* was also associated with endocrine morbidity and may serve as a practical surrogate of global iron toxicity in centers without pituitary MRI capability (Gamberini et al., 2011; Singer et al., 2021); Singer et al. (2021) reported that cardiac T2* <20 ms and liver iron concentration >10 mg/g dry weight were strongly associated with pituitary iron sufficient to cause volume loss. Serum ferritin, by contrast, showed inconsistent associations: a ferritin level above 2,500 µg/L increased the odds of hypogonadism 2.75-fold in one large cohort (Belhoul et al., 2012), whereas the difference between hypogonadal and eugonadal patients was not significant in another (Mahwi et al., 2023) (Table 4).

Table 4. Imaging and iron burden indicators

Marker	Threshold	Interpretation
Pituitary R2	Z-score >5	Severe pituitary iron; independent predictor of hypogonadism
Pituitary volume	Z-score <-2.5	Gland atrophy; independent predictor of hypogonadism
Pituitary T2*-weighted signal	Reduced	Associated with hypogonadism
Cardiac T2*	<20 ms	Associated with pituitary iron overload
Liver iron concentration	>10 mg/g dry weight	Associated with pituitary iron overload
Serum ferritin	>2,500 µg/L	Higher odds of hypogonadism; inconsistent across studies

Sources: Noetzli et al. (2012); Christoforidis et al. (2007); Singer et al. (2021); Belhoul et al. (2012); Mahwi et al. (2023). MRI, magnetic resonance imaging; R2 and T2*, MRI relaxation parameters that rise and fall, respectively, with tissue iron; Z-score, standard deviation score relative to age-matched healthy reference values.

3.7 Fertility outcomes

In an Italian multicentre series, 46 women with BTM had 58 pregnancies, 91% of which ended in live birth, and 33 conceived after gonadotropin-induced ovulation (Origa et al., 2010). Among 21 women with BTM undergoing in vitro fertilization, more gonadotropin was required than in matched controls, but the number of oocytes retrieved and the rate of top-quality embryos did not differ (Mensi et al., 2019). Few studies reported time to conception or live-birth rates, so most conclusions rest on surrogate markers rather than on fertility itself.

4. DISCUSSION

This systematic review indicates that female infertility in transfusion-dependent beta-thalassemia major is driven by a complex interplay between pituitary iron toxicity, potential direct ovarian damage, and the cumulative

effects of long-term iron burden and chelation history (Borgna-Pignatti and Gamberini, 2011; Farmakis et al., 2022; Noetzli et al., 2012; Tsilionis et al., 2024). HH emerged as the dominant mechanism, but diminished ovarian reserve was also documented in several cohorts, even without overt pituitary failure (Chang et al., 2011; Matter et al., 2026; Özcan et al., 2023; Talaulikar et al., 2019; Uysal et al., 2017). The following sections compare the predictive value of each group of indicators and examine why the included studies reach different conclusions.

4.1 Central (pituitary) mechanisms and hypogonadotropic hypogonadism

Iron deposition in the anterior pituitary remains the cornerstone pathophysiologic mechanism underlying infertility in BTM (Mahwi et al., 2023; Noetzli et al., 2012; Singer et al., 2021). Of all the indicators examined, pituitary MRI showed the most consistent association with clinical HH (Table 4), and its abnormalities often precede clinical manifestations. Imaging studies suggest that pituitary iron begins to accumulate in the first decade of life, whereas clinically significant volume loss appears in the second, and that both are associated with reduced LH and FSH secretion (Noetzli et al., 2012; Singer et al., 2021). This temporal relationship supports the concept that pituitary MRI indices serve as early biomarkers of impending reproductive failure. Their strength should nevertheless not be overstated: the proposed thresholds come from relatively small cohorts of 30-56 patients examined with different sequences, and the degree of overlap between patients with and without HH was rarely reported (Christoforidis et al., 2007; Noetzli et al., 2012; Singer et al., 2021). From a clinical standpoint, identifying women with subclinical pituitary siderosis provides an opportunity for intensified chelation and early fertility counseling before irreversible gonadotrope damage occurs (Borgna-Pignatti and Gamberini, 2011; Farmakis et al., 2022; Taher and Saliba, 2017).

4.2 Ovarian reserve and direct gonadal toxicity

The ovarian reserve data are less uniform. Multiple studies demonstrate reduced AMH, lower AFC, and decreased ovarian volume in women with BTM compared with age-matched controls (Chang et al., 2011; Matter et al., 2026; Mensi et al., 2019; Talaulikar et al., 2019; Uysal et al., 2017), suggesting that iron overload may directly impair ovarian reserve in at least a subset of patients through iron-induced oxidative stress, mitochondrial dysfunction in granulosa cells, and disruption of intraovarian signaling pathways essential for follicle survival and maturation (Roussou et al., 2013; Tsilionis et al., 2024). The inverse relationship between AMH and ferritin reported by Chang et al. (2011) supports this view. Other cohorts, however, report relatively preserved AMH despite low gonadotropins, indicating that ovarian follicle pools may remain intact in early or predominantly central hypogonadism (Singer et al., 2011). Clinically, this underscores that AMH and AFC should be interpreted in conjunction with pituitary function and iron metrics rather than in isolation (Broer et al., 2014; La Marca et al., 2010).

4.3 Explaining divergent findings across studies

Several features of the included studies help explain why their conclusions differ. First, age and cumulative iron exposure modified the results. Singer et al. (2011) found ovarian reserve largely preserved before 30-35 years, with a decline thereafter, and Talaulikar et al. (2019) documented consistently low values over a decade; yet Matter et al. (2026) already found reduced reserve in adolescents, suggesting that the duration and intensity of iron exposure matter more than age

alone. Because AMH declines with age in all women, comparisons against unmatched controls or general-population nomograms can either exaggerate or conceal a disease effect. Second, the chelation era varied widely: the incidence of endocrine complications fell over three decades in the Ferrara cohort as chelation improved (Gamberini et al., 2008), and endocrine outcomes differed by chelating agent (Poggi et al., 2016). Third, in hypogonadal women not receiving hormone replacement, AFC and ovarian volume may be low because of absent gonadotropin stimulation rather than true follicle loss, so ultrasound markers can understate the remaining reserve (Singer et al., 2011). Fourth, the populations differed: several cohorts were mixed-sex or recruited from endocrine referral clinics, which inflates prevalence estimates (Mahwi et al., 2023), and AMH assays, AFC definitions, and MRI protocols were not uniform. Taken together, conflicting results are better explained by differences in populations and methods than by the absence of an ovarian component.

4.4 Iron burden metrics and their relationship to fertility

Serum ferritin, while widely used, shows only modest and inconsistent correlations with reproductive dysfunction (Belhoul et al., 2012; Mahwi et al., 2023). In contrast, MRI-based measures, particularly pituitary MRI and cardiac T2*, provide more organ-specific risk stratification (Noetzli et al., 2012; Singer et al., 2021). Several studies suggest that cardiac T2* may serve as a practical surrogate marker for global iron toxicity and is associated with endocrine morbidity, including hypogonadism (Gamberini et al., 2011; Singer et al., 2021). In the study by Noetzli et al. (2012), pancreatic iron was the best single predictor of pituitary iron, and cardiac iron and ferritin were retained in multivariate analysis. These organs are therefore useful surrogates, but none replaces direct pituitary imaging when fertility risk is being assessed (Noetzli et al., 2012; Singer et al., 2021).

Emerging biomarkers such as non-transferrin-bound iron (NTBI) and labile plasma iron (LPI) have been linked to amenorrhea and ovarian reserve parameters, suggesting a potential role in identifying patients at risk for direct ovarian toxicity (Singer et al., 2011). At present, these measures remain primarily research tools and are not widely available in routine clinical practice.

4.5 Impact of chelation therapy

Chelation therapy is a critical modifier of reproductive outcomes. Earlier initiation, higher adherence, and use of more effective chelation regimens are associated with lower rates of hypogonadism and better preservation of fertility potential (Alkatawe et al., 2025; Berdoukas et al., 2011; Poggi et al., 2016). In an Iraqi case-control study, women with good chelation adherence had lower ferritin and higher FSH and estradiol than poorly adherent women. Historical cohorts exposed to prolonged periods of suboptimal chelation exhibit substantially higher rates of endocrine complications compared with more contemporary cohorts (Borgna-Pignatti & Gamberini, 2011; Gamberini et al., 2008). This temporal trend strongly supports the concept that reproductive dysfunction in BTM is, at least in part, preventable. Nevertheless, even in well-chelated patients, pituitary and ovarian complications can still occur, emphasizing that chelation is necessary but not always sufficient to fully protect reproductive function (Berdoukas et al., 2011; Farmakis et al., 2022). This finding reinforces the need for ongoing reproductive surveillance throughout adolescence and adulthood.

4.6 Clinical implications and fertility counseling

The findings of this review support a multidimensional approach to fertility risk assessment in women with BTM.

Reliance on menstrual history and gonadotropins alone is insufficient. Instead, optimal evaluation should integrate (1) clinical reproductive history, (2) biochemical assessment of the HPG axis, (3) ovarian reserve testing with AMH and AFC, and (4) MRI-based iron assessment, particularly of the pituitary and heart (Farmakis et al., 2022; Matter et al., 2026; Noetzli et al., 2012; Singer et al., 2021; Talaulikar et al., 2019; Tsilionis et al., 2024). This integrated model enables stratification into high-, intermediate-, and lower-risk categories, facilitating personalized counseling. Women identified at high risk, such as those with pituitary MRI abnormalities and biochemical HH, should be counseled early regarding fertility preservation and assisted reproduction options. Conversely, women with preserved ovarian reserve but evolving pituitary iron overload may benefit most from intensified chelation and close follow-up (Berdoukas et al., 2011; Farmakis et al., 2022).

4.7 Assisted reproduction and pregnancy outcomes

Encouragingly, multiple reports document successful ovulation induction, in vitro fertilization, and pregnancies in women with BTM, particularly when ovarian reserve is preserved and endocrine dysfunction is appropriately treated (Mensi et al., 2019; Origa et al., 2010). These outcomes highlight that infertility in BTM is not absolute and that proactive management can yield favorable reproductive results. However, higher gonadotropin doses may be required, and multidisciplinary management is essential to address cardiac, hepatic, and endocrine comorbidities during pregnancy (Farmakis et al., 2022; Origa et al., 2010).

4.8 Limitations and future directions

The available literature is limited by small sample sizes, heterogeneity in study design, and variability in chelation eras and protocols. Many studies are cross-sectional, limiting causal inference. Standardized cutoffs for AMH, AFC, and pituitary MRI parameters specific to BTM populations are lacking (Broer et al., 2014; La Marca et al., 2010; Noetzli et al., 2012; Singer et al., 2021). This review also has limitations of its own. Heterogeneity in designs and outcome measures precluded meta-analysis, and a narrative synthesis is open to interpretive bias. Narrative reviews and guidelines were included alongside primary studies, so some primary data may be represented more than once; several cohorts were mixed-sex; and restriction to published studies may have introduced publication bias. Future research should focus on large, prospective, multicenter studies, longitudinal evaluation of ovarian reserve trajectories, and validation of composite fertility risk scores integrating clinical, biochemical, and imaging data.

5. CONCLUSIONS

Female infertility in transfusion-dependent BTM results mainly from iron-related pituitary injury, with a variable contribution from direct ovarian damage that appears to depend on age and cumulative iron exposure. Menstrual history and gonadotropins identify established HH, AMH and AFC estimate the remaining follicle pool, and pituitary MRI can detect iron toxicity before clinical failure. Used together, these indicators allow earlier risk stratification, timely intensification of chelation, and informed counseling on fertility preservation. Standardized, BTM-specific thresholds validated in prospective multicentre cohorts are now needed.

Declarations

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