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Long-Term Gonadal and Reproductive Toxicity of Maximum-Tolerated-Dose Hydroxyurea/Hydroxycarbamide in Children with Sickle Cell Disease: A Systematic Review

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Abstract*—Background:** ***Hydroxyurea (hydroxycarbamide) is the primary disease-modifying therapy for pediatric sickle cell disease (SCD), with guidelines recommending dose escalation to the maximum tolerated dose (MTD) from as early as 9 months of age. Its long-term effect on gonadal and reproductive function in childhood-treated individuals remains inadequately characterised. This review synthesises evidence on long-term gonadal and reproductive toxicity of MTD hydroxyurea initiated in childhood or adolescence for SCD. Methods: MEDLINE (PubMed) and Cochrane CENTRAL/CDSR were searched; ClinicalTrials.gov and WHO ICTRP-affiliated registries were searched for grey literature. Embase, Web of Science, and CINAHL could not be searched directly, which was mitigated through citation-chasing. Eligible studies reported gonadal, hormonal, or reproductive outcomes in individuals with SCD who initiated hydroxyurea before age 18. Risk of bias was assessed with ROBINS-I; findings were synthesised narratively by outcome domain. Results: Eighteen observational studies met eligibility criteria; no randomised controlled trial addressed this question. Male semen and spermatogonial-histology evidence was directly conflicting: some studies showed treatment-associated impairment with partial reversibility, while histology studies generally found no hydroxyurea-specific effect once disease-related baseline abnormality was accounted for. Female ovarian-reserve evidence was similarly divided between hormonal (AMH) studies suggesting diminished reserve and the only histological study, which found no difference in follicle density. Growth and pubertal development showed consistent evidence, with no hydroxyurea-specific signal across five studies (1997–2026). No study reported long-term pregnancy, paternity, or infancy-onset outcomes. Certainty of evidence was low or very low across all domains. Conclusions: Current evidence is insufficient to determine whether childhood-initiated MTD hydroxyurea causes clinically meaningful, irreversible gonadal or reproductive harm. Findings are more reassuring where methodology is most direct (tissue histology) and more concerning where it captures active-treatment status (semen analysis, AMH). Prospective, longitudinal studies with harmonised endpoints, particularly in infancy-treated children, are urgently needed; a relevant study (SAFE, NCT07116772) is underway.

***Index Terms*—gonadal toxicity; hydroxyurea; hydroxycarbamide; fertility; sickle cell disease; systematic review.**

I. INTRODUCTION

Sickle cell disease (SCD) is the most common inherited hemoglobinopathy worldwide, and hydroxyurea (hydroxycarbamide) – a ribonucleotide reductase inhibitor that increases fetal hemoglobin production – remains its principal disease-modifying therapy. Current international guidelines recommend initiating hydroxyurea in infancy, as early as 9 months of age, and escalating to the maximum tolerated dose (MTD), typically 25–35 mg/kg/day, to maximise clinical benefit.

As a cytotoxic agent that interferes with DNA synthesis, hydroxyurea's potential gonadotoxicity has long been a concern. Animal data, including a 2007 National Toxicology Program expert panel review, found sufficient evidence that hydroxyurea causes reproductive toxicity in male mice. Translating this to children treated from infancy through adulthood is complicated by the fact that SCD itself independently impairs spermatogenesis and ovarian reserve through chronic hypoxia, oxidative stress, and recurrent vaso-occlusion – making it difficult to isolate a

hydroxyurea-specific effect from disease-related gonadal impairment that predates any treatment.

The 2022 Cochrane review of hydroxyurea for SCD [19] concluded that despite synthesising all available randomised evidence, there remains insufficient evidence regarding the drug's long-term risks, including effects on fertility and reproduction. Existing systematic reviews addressing gonadal toxicity have either focused on adults, mixed hydroxyurea's use across multiple hematological conditions (SCD, essential thrombocythemia, polycythemia vera) [20], or searched literature only through mid-2023 [21] – predating several key primary studies published in 2024–2026 that used more direct histological methodology than earlier hormonal-marker-based studies.

This review addresses that gap. Its objective is to systematically synthesise evidence specifically on long-term gonadal and reproductive outcomes in individuals with SCD who initiated hydroxyurea during childhood or adolescence, updating and extending prior syntheses with more recent primary evidence.

II. METHODS

A. Protocol and Registration

This review was conducted according to a protocol registered prospectively on PROSPERO (CRD420251238763) and is reported according to PRISMA 2020 guidelines [22]. Deviations from the original protocol are documented in a protocol amendment log, deposited alongside the PRISMA checklist and flow diagram (see Reporting Guidelines), and summarised in Section II-C below.

B. Eligibility Criteria

Studies were eligible if they reported gonadal, hormonal, or reproductive/fertility outcomes in individuals with SCD who initiated hydroxyurea/hydroxycarbamide before age 18, with human study designs including randomised controlled trials, cohort studies, case-control studies, and case series with five or more participants. Narrative reviews, editorials, conference abstracts without extractable data, animal/in vitro studies, and studies where outcomes were not attributable to hydroxyurea specifically (e.g., outcomes driven primarily by subsequent hematopoietic stem cell transplantation conditioning) were excluded.

C. Information Sources and Search Strategy

MEDLINE (via PubMed) and Cochrane CENTRAL/CDSR were searched systematically using a combination of MeSH terms and free-text keywords for hydroxyurea/hydroxycarbamide, sickle cell disease, pediatric/childhood terms, and fertility/gonadal/reproductive terms. ClinicalTrials.gov and WHO ICTRP-affiliated registries (including PACTR and ISRCTN) were searched for grey literature and ongoing trials.

1) Full search strategy: The PubMed search strategy, as logged and run on 20 August 2026, was: (“hydroxyurea”[MeSH] OR hydroxycarbamide) AND (“sickle cell disease”) AND (child OR pediatric OR adolescent) AND (fertility OR gonadal OR spermatogenesis OR azoospermia OR “ovarian reserve” OR reproduct*), with no date or language limit. The parallel Cochrane CENTRAL/CDSR search used a broader, unfiltered string (“hydroxyurea” AND “sickle cell disease”), without the fertility/gonadal filter terms.

This logged PubMed string, run in full, returned 187 records on 20 August 2026 — a larger yield than the 68 PubMed records carried through the PRISMA tracking log (dated 17 August 2026, one day earlier), which appears to reflect an earlier or more restricted batch rather than the string above. This discrepancy in the search record is disclosed as an additional documentation gap (Section IV-D) rather than resolved retrospectively. The full search log, including the ClinicalTrials.gov and WHO ICTRP-affiliated registry strategies, is deposited alongside the PRISMA checklist and flow diagram (see Reporting Guidelines).

Embase and Web of Science Core Collection could not be searched directly due to institutional access limitations; this was mitigated through backward and forward citation-chasing of all included studies, and through reference-mining of two adjacent systematic reviews identified during screening (Cilio et al. [20], covering hydroxyurea and male fertility across SCD/essential thrombocythemia/polycythemia vera; Silva et al. [21], covering functional ovarian reserve in

SCD), both of which had themselves searched PubMed, Embase, and Cochrane through their respective cutoffs. This reference-mining identified two additional eligible primary studies not captured by the direct PubMed search. CINAHL was not searched, reflecting its focus on nursing and allied-health literature and the corresponding low expected marginal yield for hematology/andrology primary studies; this is acknowledged as a limitation (Section IV-D).

D. Study Selection, Data Extraction, and Risk of Bias

Records were screened at title/abstract and full-text stages against the eligibility criteria above. Data were extracted into a structured form capturing study design, population characteristics, hydroxyurea dosing and duration, comparator group, outcome measures, and key findings. Risk of bias was assessed using the ROBINS-I tool for non-randomised studies, since no eligible randomised controlled trial was identified. Screening, data extraction, and risk-of-bias assessment were performed by a single reviewer (U.N.M.); the absence of independent dual review at any stage is acknowledged as a limitation of this review (Section IV-D).

E. Data Synthesis

Given substantial heterogeneity in outcome measures (semen parameters, hormonal assays, histological markers, pubertal staging) and study designs across included studies, findings were synthesised narratively, structured by outcome domain, in line with the pre-specified protocol. Meta-analysis was not attempted; consequently, no summary effect measures (e.g., pooled risk ratios or mean differences) were calculated, and this PRISMA item is not applicable. Formal assessment of reporting bias (e.g., funnel plots or statistical tests for small-study effects) was not conducted, given the small number of studies within each outcome domain; this is acknowledged as a limitation (Section IV-D).

F. Certainty of Evidence Assessment

Certainty of evidence for each outcome domain was assessed using an approach informed by the GRADE framework, considering risk of bias (based on the ROBINS-I ratings in Section II-D), consistency of findings across studies within the domain, directness of the evidence to the review question, and precision (informed by sample size and the consistency of effect direction). Certainty was not formally rated using GRADEpro software; ratings and the primary reasons for downgrading are presented narratively for each domain in Section III-E.

III. RESULTS

A. Study Selection

The PubMed (n = 68) and Cochrane CENTRAL/CDSR (n = 20) searches identified 88 records for title/abstract screening. Following title/abstract screening, 39 records were excluded (19 from PubMed; 19 from Cochrane as topically unrelated; 1 Cochrane record [CD002202, Rankine-Mullings & Nevitt [19]] already captured as a background source). A total of 28 records proceeded to full-text assessment (11 clear includes at the title/abstract stage, plus 17 requiring full-text review to confirm eligibility); the screening log does not record a final disposition for the remaining 21 records, which is disclosed as a documentation gap in Section IV-D. Of the 17 full-text 'maybe' records, 11 were excluded (3 for unconfirmed pediatric-onset population, 3 for being reviews rather than primary studies, 2 for reporting counseling/procedural rather than gonadal-toxicity outcomes, 1 for reporting outcomes attributable to transplant conditioning rather than hydroxyurea, 1 for an underpowered mechanistic subgroup, and 1 for insufficient hydroxyurea-specific data) and 5 were included; the final disposition of the remaining 1 record is likewise not recorded (Section IV-D). Grey literature searching of ClinicalTrials.gov identified 5 additional records, none meeting inclusion criteria at present (one ongoing prospective study, NCT07116772, is directly relevant but has not yet reported results). Citation-chasing and reference-mining of two adjacent systematic reviews (Cilio et al. [20], covering male fertility across SCD/essential thrombocythemia/polycythemia vera; Silva et al. [21], covering female ovarian reserve in SCD) identified two further eligible primary studies not captured by direct screening (Grigg [2]; Portela et al. [6]). In total, 18 primary studies were included in the qualitative synthesis (16 from database/register screening; 2 from citation-chasing).

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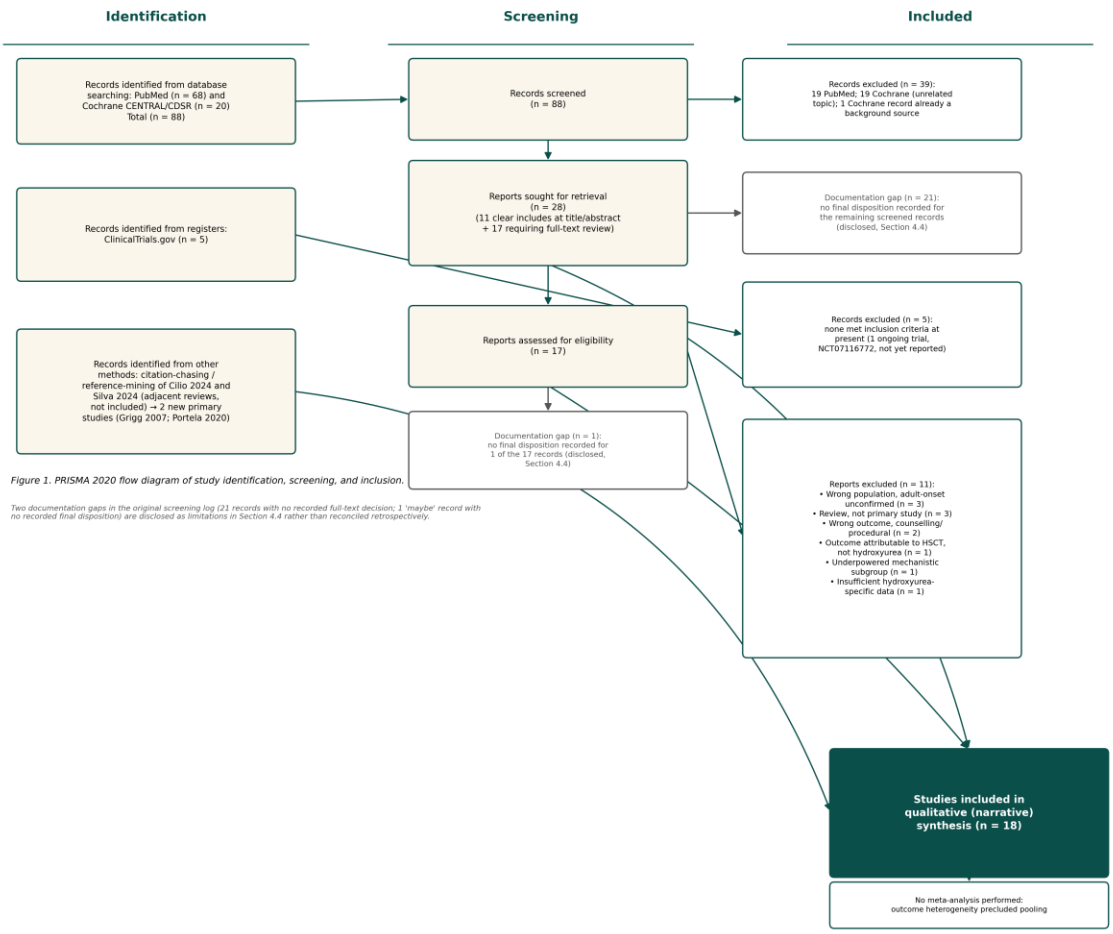

Fig. 1. PRISMA 2020 flow diagram of study identification, screening, and inclusion.

B. Study Characteristics

All 18 included studies were observational: prospective cohorts (n=5), retrospective cohorts (n=6), cross-sectional histological comparisons (n=5), and small case series (n=2, with overlap in classification for mixed designs). Publication years ranged from 1997 to 2026. Sample sizes ranged from 3 to 606 participants. No randomised controlled trial directly addressing gonadal or reproductive outcomes of childhood-initiated hydroxyurea was identified. Study characteristics are summarised in Table I.

TABLE I
STUDY CHARACTERISTICS (N = 18)

Study	Design	n	Outcome Domain
Wang et al., 2002 (HUG-KIDS) [1]	Prospective cohort (trial)	68	Growth/puberty
Grigg, 2007 [2]	Retrospective case series	4	Semen parameters
Berthaut et al., 2008 [3]	Retrospective cohort	44	Semen parameters
Lukusa & Vermylen, 2008 [4]	Case series	4	Semen parameters
Lukusa et al., 2009 [5]	Retrospective comparative	10	Semen + hormones
Portela et al., 2020 [6]	Cross-sectional histology	3 (of 18 total)	Spermatogonial quantity

Study	Design	n	Outcome Domain
Sahoo et al., 2017 [7]	Prospective cohort	100	Semen parameters
Elchuri et al., 2015 [8]	Case-control	56	Ovarian reserve
Hankins et al., 2014 (HUSOFT ext.) [9]	Prospective cohort	8	Growth/puberty
Nagalapuram et al., 2019 [10]	Retrospective cohort	157	Growth/puberty
de Montalembert et al., 1997 [11]	Prospective uncontrolled	35	Growth/puberty
Joseph et al., 2021 [12]	Cross-sectional comparative	38	Semen parameters
Gille et al., 2021 [13]	Cross-sectional histology	30	Spermatogonial quantity
Stukenborg et al., 2018 [14]	Cross-sectional histology	6 (of 32 total)	Spermatogonial quantity
Masliukaite et al., 2023 [15]	Retrospective histology	SCD subgroup	Spermatogonial quantity
George et al., 2022 [16]	Retrospective cohort	17	Ovarian reserve
Diesch-Furlanetto et al., 2024 [17]	Retrospective histology	76	Ovarian reserve
Backeljauw et al., 2026 (REACH) [18]	Prospective cohort (trial)	606	Growth/puberty/hormones

C. Risk of Bias

One study (Wang et al. [1]) was rated overall low risk of bias. Nine studies were rated moderate risk, primarily reflecting referral-based selection bias inherent to fertility-preservation cohorts and the absence of concurrent comparator groups. Eight studies were rated serious risk, primarily small case series without denominators, or studies where hydroxyurea's independent contribution could not be isolated from confounders such as concurrent transfusion therapy or subsequent transplant conditioning. No study was rated critical risk of bias, as summarised in Fig. 2.

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Fig. 2. Risk-of-bias assessment (ROBINS-I) for all 18 included studies, by domain.

D. Synthesis by Outcome Domain

1) Male semen parameters: Five studies assessed semen parameters. Findings were directly conflicting. Berthaut et al. [3] found that all semen parameters worsened within six months of hydroxyurea initiation across 44 patients (108 samples), with only partial recovery after discontinuation in 30 of 44 patients and persistent impairment in four. Sahoo et al. [7] reported that even low-dose hydroxyurea (10 mg/kg/day) was associated with increased azoospermia during treatment (10% vs. 4% untreated), with 73% reverting to normal after a three-month cessation. Grigg [2], in a small case series, reported reduced sperm count and motility in all four patients during treatment, with recovery in only one of three cases with cessation data. In contrast, Joseph et al. [12] – the only study directly comparing men with prepubertal-onset hydroxyurea exposure (median age 6 years at initiation, since discontinued) against hydroxyurea-naive patients – found no significant difference in any semen parameter, with no correlation between semen quality and age of onset, dose, or treatment duration.

This apparent contradiction may reflect treatment status at the time of assessment: studies capturing active treatment (Berthaut [3], Sahoo [7], Grigg [2]) reported impairment, while the study assessing patients after discontinuation (Joseph [12]) found no residual difference – a pattern consistent with substantially reversible, treatment-associated suppression rather than fixed damage, though this cannot be confirmed with confidence for decades-long childhood-onset exposure specifically.

2) Male spermatogonial quantity (histological studies): Four studies used direct testicular histology in prepubertal boys, the only method capable of assessing gonadal status before puberty. These four studies did not agree. Gille et al. [13] found no significant difference in spermatogonia per tubular

cross-section between 13 hydroxyurea-naive and 17 hydroxyurea-exposed boys (p=.52); both groups had lower counts than healthy reference values. Masliukaite et al. [15] similarly found comparable rates of reduced spermatogonial quantity in hydroxyurea-exposed (58.3%) and hydroxyurea-naive (50%) boys with SCD, implicating disease rather than drug. Portela et al. [6] found no difference in spermatogonial density between three hydroxyurea-treated SCD patients and orchiectomy-tissue controls, but did find a significantly reduced maturation marker (5mC-positive spermatogonia) specific to the SCD-hydroxyurea group (p<.016). In contrast, Stukenborg et al. [14] found a significant reduction in spermatogonial quantity in six hydroxyurea-exposed boys compared with 14 biobank controls (p=.008).

Three of four studies suggest sickle cell disease itself, rather than hydroxyurea specifically, is the primary driver of reduced prepubertal spermatogonial numbers, consistent with well-documented SCD-related sperm abnormality independent of treatment. The Portela finding raises the possibility of a more specific, subtle maturational deficit not captured by simple density counts, which may partially reconcile the disagreement, but this requires replication.

3) Female ovarian reserve: Two studies directly addressed female ovarian reserve, using different methodologies with divergent findings. Elchuri et al. [8] found diminished ovarian reserve (AMH below the 5th percentile) in 24% of hydroxyurea-treated girls and young women, compared with 100% in a bone-marrow-transplant comparator group. Diesch-Furlanetto et al. [17] – the only study to measure ovarian reserve directly via follicle-density histology rather than the AMH proxy, in a cohort where 65.8% of participants were prepubertal – found no significant difference in primordial follicle density between hydroxyurea-exposed and hydroxyurea-naive girls (5.8 vs. 4.2 follicles/mm2, p=.95). The Backeljauw et al. [18] REACH cohort found AMH low in only 3.6% of girls at baseline, rising marginally to 5.1% at follow-up, a smaller effect than Elchuri's cross-sectional estimate. As in the male histological literature, the direct tissue-based evidence was more reassuring than the hormonal-marker evidence.

4) Hormonal profiles: George et al. [16] found that among girls who had received hydroxyurea prior to hematopoietic stem cell transplantation, AMH was normal in 88% (15 of 17) immediately before transplant conditioning began, suggesting hydroxyurea alone had not driven abnormal ovarian reserve in this small cohort prior to subsequent alkylating exposure. In the REACH cohort [18], boys' AMH improved on treatment (52% low at baseline to 28% at follow-up) – the opposite direction from what gonadotoxicity would predict, though this was not the study's primary comparison and should be interpreted cautiously.

5) Growth and pubertal development: Five studies spanning 1997 to 2026 assessed growth and pubertal development, and showed the most internally consistent findings of any domain. Wang et al. [1] (HUG-KIDS) found no significant adverse effect on height, weight, or Tanner-stage progression over one year of treatment. Hankins et al. [9] (HUSOFT extension) reported that puberty occurred without delay (ages 10–14) and growth was sustained at the 50th percentile over 15 years of continuous treatment beginning in infancy. de Montalembert et al. [11] found growth curves and clinical sexual development were not modified over three years of treatment. Backeljauw et al. [18] (REACH) found puberty delayed in 25–30% of children, but attributed this to SCD itself rather than hydroxyurea, consistent with known disease-related pubertal delay; delayed puberty progressed on treatment. Nagalapuram et al. [10] found no significant difference in peak height velocity between hydroxyurea-treated and untreated children. No study identified a hydroxyurea-specific adverse effect on growth or pubertal timing distinct from the disease's own known effects.

E. Certainty of Evidence

Certainty of evidence, assessed as described in Section II-F, is summarised by outcome domain in Table II.

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TABLE II
CERTAINTY OF EVIDENCE BY OUTCOME DOMAIN

Outcome Domain	Certainty	Primary Reasons for Downgrading
Growth/pubertal development	Low	Observational designs; consistent direction of effect across 5 studies over three decades
Male semen parameters	Very low	Directly conflicting findings; serious confounding by baseline disease-related abnormality and concurrent transfusion; small samples
Male spermatogonial quantity	Very low	Directly conflicting studies; referral-based selection bias; very small per-group samples (n=3–17)
Female ovarian reserve	Very low	Only 2 primary studies with conflicting methodologies; very small samples
Hormonal profiles	Very low	Single longitudinal cohort; confounded by subsequent transplant conditioning in one study

Risk of bias due to missing results (reporting bias) was not formally assessed for any outcome domain; no funnel plots or statistical tests for small-study effects were conducted, given the small number of studies within each domain (Section II-E).

IV. DISCUSSION

A. Principal Findings

This systematic review identified 18 observational studies addressing gonadal and reproductive outcomes of childhood-initiated hydroxyurea in SCD. Evidence was directly conflicting for male semen parameters and spermatogonial histology, and for female ovarian reserve, with a consistent pattern: studies using direct tissue histology were more reassuring than studies using hormonal markers (AMH) or semen analysis performed during active treatment. Growth and pubertal development showed the most consistent evidence, with no study identifying a hydroxyurea-specific adverse effect distinct from SCD's own known effects on growth and puberty. No outcome domain achieved better than low certainty of evidence.

B. Comparison with Existing Literature

These findings extend and partially update the 2022 Cochrane review's [19] conclusion that evidence on hydroxyurea's long-term fertility risks remains insufficient, incorporating primary studies published through 2026 that were not available at the time of that review, including the histological studies (Diesch-Furlanetto [17], Masliukaite [15]) that provide the most direct evidence to date on this question. This review's more pediatric-onset-specific eligibility criteria also differentiate it from Cilio et al. [20] and Silva et al. [21], both of which addressed overlapping questions across broader age ranges and, in Cilio's case, across multiple hematological conditions beyond SCD.

C. Interpretation

The recurring pattern across both male and female gonadal outcomes – reassuring histological findings alongside more concerning hormonal or active-treatment functional findings – admits at least two interpretations. First, hydroxyurea may cause genuinely reversible, treatment-associated functional suppression that resolves without permanent structural loss, in which case histology (a structural measure) and hormonal/functional assays (a status measure) would be expected to diverge exactly as observed. Second, methodological limitations specific to each approach – selection bias in referral-based fertility-preservation histology cohorts, or the known limitations of AMH as an ovarian reserve proxy in chronic inflammatory disease – could independently explain the discrepancy without any true biological reconciliation. This review's evidence base cannot distinguish between these explanations.

D. Strengths and Limitations

This review's principal strength is its focused, pediatric-onset-specific eligibility criteria and its incorporation of the most recent (2024–2026) primary

evidence, including direct histological studies not available to prior syntheses. Its principal limitations concern search comprehensiveness: Embase and Web of Science Core Collection could not be searched directly due to institutional access constraints and were substituted with citation-chasing, which, while it did surface two additional eligible studies, cannot fully guarantee the same coverage as direct database searching. CINAHL was not searched. Screening, extraction, and risk-of-bias assessment were also conducted by a single reviewer without independent dual verification, which may have introduced unquantified error or selection bias relative to reviews using paired reviewers. The screening log also contains two unresolved documentation gaps, disclosed here rather than reconciled retrospectively: (i) of the 49 PubMed and Cochrane records that were not excluded at title/abstract screening, only 28 have a recorded full-text decision, leaving 21 records with no final disposition; (ii) of the 17 full-text records flagged as requiring confirmation, 11 exclusions and 5 inclusions are recorded, leaving 1 record with no final disposition; and (iii) the PubMed search string as logged returned 187 records when run in full, yet only 68 PubMed records are carried through the tracking log, suggesting the tracked batch reflects an earlier or narrower run rather than the logged string. These gaps reflect incomplete logging during single-reviewer screening rather than a known exclusion decision, and it is possible, though not confirmed, that one or more eligible studies were missed as a result. The included evidence base itself is limited by small sample sizes, heterogeneous outcome definitions, absent or historical comparator groups, and referral-based selection bias in the histological studies; no meta-analysis was possible given this heterogeneity.

E. Implications for Research and Practice

No included study assessed gonadal outcomes following hydroxyurea initiated during infancy or the minipuberty window (age under 3 years), despite this being the guideline-recommended age of initiation since 2014. This represents the most clinically urgent evidence gap: counseling for the youngest-treated cohort of children currently has no direct evidence base. No study reported long-term pregnancy, paternity, or live-birth outcomes specifically in patients whose exposure began in childhood. A prospective, international, longitudinal study designed to address these exact gaps (the SAFE study, NCT07116772) is currently recruiting participants from age 8 across sites in Cincinnati, the Dominican Republic, Jamaica, and Tanzania, with results anticipated through 2035; its design is consistent with, and anticipates, the gaps identified by this review.

Pending more definitive evidence, clinicians counseling families about hydroxyurea initiation in childhood should communicate genuine uncertainty regarding long-term gonadal outcomes, distinguishing this from the well-established and more consistent evidence base supporting hydroxyurea's efficacy in reducing SCD-related morbidity and mortality.

V. CONCLUSION

Current evidence is insufficient to determine whether maximum-tolerated-dose hydroxyurea initiated in childhood causes clinically meaningful, irreversible gonadal or reproductive harm in individuals with sickle cell disease. The most methodologically direct evidence – tissue histology – is the most reassuring, while hormonal and active-treatment functional evidence raises genuine concern that cannot be dismissed. Growth and pubertal development, by contrast, show a consistent absence of hydroxyurea-specific harm. Prospective, adequately powered, longitudinal studies with harmonised semen, ovarian-reserve, and pregnancy-outcome endpoints – particularly in children treated from infancy – remain the field's most pressing unmet need.

DATA AVAILABILITY

Underlying data: All data underlying the results are available as part of the article and no additional source data are required. The full list of included studies, their characteristics, risk-of-bias judgements, and outcome-domain synthesis are presented in Section III and Tables I–II.

REPORTING GUIDELINES

This review is reported in accordance with the PRISMA 2020 statement [22]. The completed PRISMA 2020 checklist, PRISMA flow diagram (Fig. 1), and protocol amendment log for this review are deposited at: Zenodo. PRISMA 2020 checklist, flow

diagram, and protocol amendment log for 'Long-Term Gonadal and Reproductive Toxicity of Maximum-Tolerated-Dose Hydroxyurea/Hydroxycarbamide in Children with Sickle Cell Disease: A Systematic Review'. https://doi.org/10.5281/zenodo.22341580. Data are available under the terms of the Creative Commons Attribution 4.0 International licence (CC BY 4.0).

COMPETING INTERESTS

No competing interests were disclosed.

GRANT INFORMATION

The author(s) declared that no grants were involved in supporting this work.

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The author used Claude (Anthropic), an AI-based large language model, for technical and organisational assistance in reformatting the manuscript to IRE Journals submission requirements. Claude was not used to generate the scientific content, analysis, interpretation, or conclusions of this review; all extracted data, evidence synthesis, and conclusions are the author's own and were independently verified by the author against the underlying screening and extraction records.

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