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Systematic Review

Clinical Reproductive Outcomes Associated with Male Diabetes and Glycemic Status: A Systematic Review by Stage of Reproductive Care

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Abstract

Background/Objectives: Evidence linking paternal diabetes and glycemic status to reproductive outcomes arises from different clinical populations. We assessed how study entry and outcome denominators affect interpretation. Methods: Seven databases were searched on 3–4 September 2026 for comparative human studies. We extracted exposure definitions, eligibility criteria, analysis units, outcomes, and certainty of evidence. An expansion of PROSPERO registration CRD420261467987 became public on 19 September 2026. Results: Twenty-four reports represented 19 study families; seven potentially relevant reports were unavailable. Childhood-onset type 1 diabetes was associated with a lower rate of first live-born children (hazard ratio 0.77, 95% confidence interval 0.72–0.83). In infertility care, type 2 diabetes was associated with more surgical sperm retrieval (adjusted odds ratio 4.80, 95% confidence interval 3.24–7.12), but cumulative live birth after completed treatment courses was uncertain (adjusted odds ratio 0.81, 95% confidence interval 0.59–1.11). After single-blastocyst frozen-thawed transfer, the highest versus lowest paternal fasting-glucose quartile had lower live-birth odds (adjusted odds ratio 0.64, 95% confidence interval 0.43–0.95). Sixteen out of 19 certainty profiles were low or very low. Conclusions: Estimates apply to populations reaching different care milestones. Evidence does not establish live-birth prognosis from treatment initiation or fertility-specific glycemic targets.

Keywords: diabetes mellitus; male infertility; reproductive endocrinology; live birth; assisted reproductive technology; glycemic status

1. Introduction

The relevance of paternal diabetes to reproduction depends on when couples enter observation. Before conception, the main questions concern fecundability and eventual fatherhood. At an infertility consultation, couples may wish to know their prospects from the start of treatment, including cancellation or discontinuation. Estimates restricted to embryo transfers or recognized pregnancies describe narrower populations. Partner characteristics and treatment decisions influence progression through care [1,2], and selection on intermediate events can alter observed associations [3–5]. Clinical interpretation therefore requires the source population, denominator, and analysis unit of each estimate.

An observational meta-analysis linked diabetes in men to lower semen volume and motility, with no clear difference in total sperm count [6]. Subsequent reviews reported inconsistent associations with morphology and sperm DNA fragmentation [7,8]. These findings offer biological context but do not directly measure conception or live birth. Other

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reviews have addressed reproductive physiology, fertility, paternal preconception health, and medication exposure [9–14]. Female diabetes is associated with menstrual and ovulatory disorders, subfertility, and pregnancy complications [15]. Female-partner metabolic status and infertility diagnoses may also influence both treatment entry and outcomes. We therefore distinguished eligibility restrictions, matching, and statistical adjustment for partner factors (Table S17).

This review examined the clinical applicability of reported associations between male diabetes or glycemic status and reproductive outcomes. We recorded paternal exposures, study entry criteria, outcome definitions, denominators, analysis units, partner-related factors, and evidence certainty. We distinguished population and conception-attempt estimates from outcomes conditional on treatment, transfer, or pregnancy. The resulting categories describe source-study populations rather than a validated clinical staging system.

2. Materials and Methods

2.1. Review Design, Registration, and Eligibility

We followed the PRISMA 2020 and PRISMA-S [16,17], with relevant SWiM guidance informing the structured synthesis [18]. PROSPERO registration CRD420261467987 initially covered paternal type 2 diabetes mellitus (T2DM) and IVF/ICSI outcomes. At an in-person research-team meeting on 3 September 2026, the corresponding author approved piloting a broader question involving other paternal glycemic exposures and clinical reproductive outcomes before and after infertility treatment. According to the authors' retrospective account, the team reran PubMed on 4 September using the search expression later retained for the review. During this pilot, the team examined retrieved records, selected full texts, and some reported effect estimates or statistical results. All authors then discussed and confirmed the expanded eligibility criteria on 4 September and applied the agreed criteria across all database records. These decisions are described from the authors' recollection because no contemporaneous meeting minutes or signed amendment record were retained; archived PubMed primary-route searches are dated 3 September, and no separate export of the reported 4 September rerun was located. As some results were examined before final agreement, result-informed scope selection cannot be excluded. A PRESS review record dated 3 September documents broader search concepts but is not an independent record of protocol approval. The final seven-database searches were conducted on 3–4 September 2026, whereas the expanded scope became publicly visible in PROSPERO version 3 on 19 September 2026. The latter was therefore a retrospective public registration update, rather than prospective registration of the broader question. The broader scope allowed outcomes measured before treatment to be distinguished from those conditional on embryo transfer or an established pregnancy. The version 3 form still listed Google Scholar and PROBAST, whereas the completed review used WanFang among the seven databases and ROBINS-E/JBI appraisal. The amendment chronology and differences between the registered and executed methods are detailed in Table S1 and Appendix S27.

We included comparative human studies reporting an identifiable paternal diabetes or glycemic exposure and at least one clinical reproductive endpoint: fecundability or time to pregnancy, realized fatherhood, clinically defined infertility, treatment use, pregnancy loss, live birth, or cumulative live birth. Exposures included type 1 diabetes mellitus (T1DM), T2DM, unspecified diabetes, prediabetes, fasting glucose, and glycated hemoglobin (HbA1c). Male-, female-, and mixed-factor infertility populations were eligible when a paternal exposure comparison could be identified. Studies restricted to semen, molecular laboratory outcomes, or sexual-function questionnaire scores were excluded from clinical synthesis; the last distinction was not specified prospectively in the original public protocol. Explicitly observed zero events were separated from unmeasured, missing, or

unreported outcomes. Conditional outcomes used only participants reaching the relevant treatment or pregnancy milestone. Source-specific gestational definitions were preserved (Table S30).

2.2. Search, Selection, and Extraction

PubMed, Embase, Web of Science Core Collection, CENTRAL, SinoMed, CNKI, and WanFang were searched on 3–4 September 2026 without date or language restrictions, yielding 29,199 records. Duplicate records were identified using EndNote 2025 and manual comparison. A documented PRESS-informed assessment of the draft PubMed strategy on 3 September prompted additional pregnancy-loss and glycemic terms [19]. Reference lists, forward citations, and targeted PubMed sensitivity searches were tracked separately, including a 12 September addendum. No study-register search or named validated filter was used. The identity of the initial search reviewer and an independent PRESS assessment across all seven databases were not documented (Appendices S1 and S27).

Two reviewers independently screened 22,624 deduplicated records, and their initial record-level decisions are archived. The final eligibility criteria were applied to the entire final-search set rather than only to selected reports. Two historical full-text worksheets recorded assessments of 55 candidates, including reports awaiting retrieval. Five additional reports were obtained later, and their final dispositions were checked by the submitting author; reviewer-specific final forms and reconciliation records were unavailable for some of these later reports. Exact-citation and PMID checks recorded on 2 November 2026 did not obtain seven distinct full texts. An additional check of PubMed citations and publicly accessible abstracts or repository records on 9 November confirmed the identity of all seven reports but did not locate complete articles in the sources examined. This represents eight route-specific unsuccessful retrieval entries because one report was identified through two routes (Table S19b). According to the submitting author, a university librarian was contacted by email on 2 November 2026 who checked the library holdings without locating the seven full texts. An author of that same report was emailed at approximately the same time and had not replied by the time of this revision. Copies of these communications were not independently inspected; formal interlibrary-loan transactions and exhaustive archival access were not documented. Eligibility was left unresolved; these reports were neither counted as full-text exclusions nor assigned imputed outcomes. Their identities, accessible evidence, retrieval limitations and potential relevance are listed in Supplementary Table S19a,b and the StillUnretrieved7 worksheet of Supplementary Data S1. We extracted exposures, comparators, outcomes, denominators, event counts, effect estimates, adjustment sets and analysis units (Tables S16–S19; Supplementary Data S1). The final ledger comprised 71 route-specific retrieval entries, 63 full-text assessments, 39 exclusions, and 24 included reports representing 19 study families. Five forward-citation exclusions were available only as aggregate counts. Figure 1, Tables S12, S13 and S19–S19b, and Appendices S28 and S32 document the selection and retrieval accounting.

2.3. Risk-of-Bias Assessment and Certainty Methods

Risk of bias was evaluated for individual results using ROBINS-E for nonrandomized exposure studies [20] and design-appropriate JBI instruments for cross-sectional and case–control studies [21,22]. Outcome-specific evidence certainty was recorded using GRADE guidance [23,24]. Original reviewer assessments, subsequent author verification, and presentation checks are distinguished in Table S8, Appendices S24 and S29. When the coding of a published adjusted estimate was uncertain, its archived rating was not assigned to a separately calculated crude contrast. Publications with overlapping participants were linked rather than counted as independent studies.

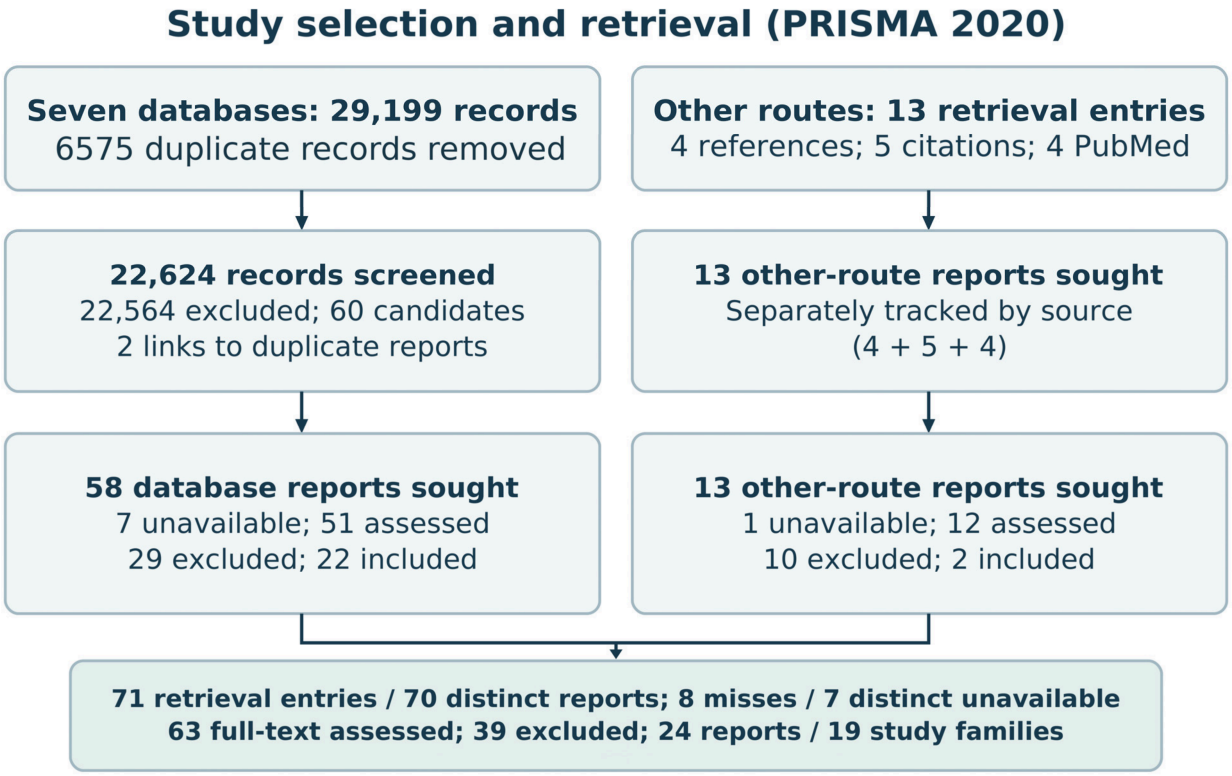


Figure 1. PRISMA 2020 study-selection and retrieval flow. Seventy-one retrieval entries represent 70 distinct reports; eight unsuccessful attempts correspond to seven unavailable reports because one report appeared in two search streams (Table S19b). The associated selection records and updates are documented in Tables S12, S13 and S19 and Appendix S28.

2.4. Reproductive-Stage Classification

We classified each evidence body by the earliest milestone required for inclusion in the original analysis: S0, population/preconception; S1, entry into infertility care; S2, treatment initiation; S3, embryo transfer; S4, biochemical pregnancy; S5, clinically confirmed pregnancy; S6, explicitly ongoing pregnancy; and S7, later gestation. U indicates claims-recognized pregnancy without a verifiable clinical recognition stage. The Kasman claims cohort was classified as U [25], whereas Yang 2023 began with ultrasound-confirmed singleton pregnancies (S5) [26]. Treatment completion, successful sperm retrieval, and evaluable samples were recorded as additional restrictions. In the linked Hervás reports, the 2021 cohort was assigned to S2 and the 2025 donor-oocyte cohort was transfer-conditioned (S3) [27,28].

2.5. Statistical Analysis and Structured Synthesis

Published odds ratios (ORs), risk ratios (RRs), hazard ratios (HRs), incidence rate ratios (IRRs), and fecundability odds ratios were retained with confidence intervals. Crude ORs were calculated only when compatible counts and denominators were available [29]; missing or unreported outcomes were not coded as zero. Results were organized by exposure, entry milestone, endpoint, and analysis unit. Four post-ART pregnancy-loss studies differed in population and potential repeated observations within couples, so individual estimates were emphasized; archived REML–Hartung–Knapp and leave-one-out calculations were treated as exploratory (Table S20). Two-sided Pearson chi-squared, Fisher exact, and Wald calculations were used when appropriate to check aggregate counts and reported significance levels. Checks used Python 3.12.14, NumPy 2.3.5, and SciPy 1.17.0; the archived exploratory REML–Hartung–Knapp analysis was rerun in Python 3.13.5. Methods and

discrepancies are recorded in Appendices S31–S33. Published adjusted models were not refitted using aggregate data.

2.6. Reproducibility and Source Verification

Source definitions and evidence tables were verified by the authors against available primary reports and archived records (Appendix S33). All database searches, study screening, data extraction, appraisal, numerical and code checks, and scientific interpretation were undertaken by the authors. ChatGPT (OpenAI; GPT-6) was used to organize author-supplied materials, prepare reference checklists and workflow templates for manual verification, assist with figure and table construction and formatting, and edit English-language presentation. Abstract-level information was not used to make definitive full-text eligibility decisions.

3. Results

3.1. Included Reports and the Evidence Available for Clinical Interpretation

Twenty-four reports from 19 linked study families were included (Figure 1). The seven-database search supplied 22 reports; reference-list screening and targeted PubMed searching contributed one each. No additional eligible report arose from forward citation searching. Seventy-one retrieval entries represented 70 distinct reports, including eight unsuccessful attempts concerning seven unavailable reports. Of the 63 assessed full texts, 39 were excluded. Related Boeri abstracts and the full article were treated as one study family. Report identities, exclusions, and outcome denominators are detailed in Tables S12, S13 and S16–S19.

Study Populations, Analysis Units and Overlapping Reports

The included studies analyzed men, couples, completed treatment courses, embryo transfers, pregnancies, or offspring records; these units cannot be combined into a single patient total (Table S16). Wang R et al. analyzed 106 couples with paternal T2DM and 212 comparators after 23 of the 129 identified T2DM men had cancelled ART [30]. Liu et al. reported retrieval procedures in 293 versus 1169 couples and cumulative live birth in 273 versus 1086 completed courses [31]. LIFE enrolled 14 men reporting diabetes and 487 comparators [32], whereas Yang et al. studied 29 versus 341 ultrasound-confirmed singleton pregnancies [26]. The Danish ART registry recorded 101,875 transfers [33], and Kasman et al. analyzed 958,804 pregnancy observations without diabetes-specific denominators [25]. Wiebe et al. reported 3010 affected and 801 unaffected siblings of both sexes, with a paired analysis of 584 families [34]. Linked Hervás reports, historical comparators, and repeated treatment cycles were not added as independent participants [27,28,35].

3.2. Where the Included Studies Began Observation

Nine evidence bodies covered population, conception-attempt, or infertility-care settings (S0–S2); nine began at transfer or a defined pregnancy milestone (S3–S7); and one included claims-recognized pregnancies of uncertain stage (U; Figure 2). The S0 category itself encompassed distinct designs, including conception-attempt cohorts and fatherhood registries. Yang reported live birth and miscarriage in the same 370 pregnancies, while other studies restricted analysis to completed treatment or successful sperm retrieval. Thus, the 19 evidence bodies do not represent 19 independent cohorts or a continuous clinical pathway.

Which patients does each estimate represent?

Evidence body and outcome	Earliest entry and restriction	GRADE
G2-10 Diabetes / fecundability	S0: couples attempting conception	Low
G2-11 T2DM / infertility prevalence	S0: community ascertainment	Very low
G2-12 HbA1c / infertility history	S0: registry questionnaire	Very low
G2-13 T1DM / realized fatherhood	S0: population or sibling follow-up	Moderate
G2-16 Diabetes / retrograde ejaculation	S0: evaluable assessment	Very low
G2-15 Prediabetes / azoospermia	S1: primary infertility clinic	Very low
G2-14 T2DM / retrieval use	S2: infertility / ART care	Low
G2-04 T2DM / cumulative live birth	S2: completed treatment only	Low
HERVAS Diabetes / TESE–ICSI live birth	S2*: retrieval success; H25 at S3	Very low
G2-08 High-normal FPG / live birth	S3: embryo transfer	Low
G2-01 T2DM / pregnancy loss	S5: clinical pregnancy	Very low
G2-02 High-normal FPG / miscarriage	S5: clinical pregnancy	Low
G2-03 Hyperglycemia / miscarriage [a]	S5: singleton pregnancy (Yang)	Moderate†
G2-05 T2DM / live birth	S5: clinical pregnancy	Very low
G2-06 T1DM / live birth	S5: clinical pregnancy	Low
G2-07 Other diabetes / live birth	S5: clinical pregnancy	Very low
G2-09 Hyperglycemia / live birth [a]	S5: same Yang pregnancies	Moderate†
WIN Diabetes / late loss or stillbirth	S7: later gestation records	Low
KASMAN Diabetes / pregnancy loss	U: claims-recognized pregnancy	Low

[a] Complementary outcomes in the same 370 pregnancies; no independent replication.
* H21 is retrieval-selected; H25 is donor-oocyte and transfer-conditioned.
† Archived adjusted-model rating; does not rate the crude binary contrast·
19 evidence bodies are not 19 independent cohorts. Labels are not a patient pathway.

Figure 2. Earliest study-entry milestone, additional eligibility restrictions, and GRADE certainty for 19 evidence bodies. Categories describe populations, not a longitudinal care pathway. Yang's two outcomes share the same 370 pregnancies; dagger-marked Moderate ratings apply to archived adjusted estimates, not the crude binary comparison. The linked Hervás body includes treatment-stage and transfer-conditioned populations.

3.3. Before or at Infertility-Care Entry: Fecundability, Infertility and Fatherhood

Evidence from conception attempts was sparse. In LIFE, 14 men reported diabetes and 487 served as comparators; the couple-based fecundability OR was 0.383 (95% CI 0.149–0.986; low certainty) [32]. A T1DM registry received responses from 2171 out of 3955 eligible men at year 5; 33 (1.5%) reported prior difficulty conceiving or an abnormal fertility test. The age-adjusted association with HbA1c was imprecise (OR 1.03, 95% CI 0.77–1.37; very low certainty), with uncertain exposure timing [36]. A community comparison of 225 men with T2DM and 632 controls yielded a crude infertility OR of 1.74 (95% CI 1.25–2.42; very low certainty), without verifiable adjustment [37]. Boeri's studies enrolled men already receiving infertility care [38,39]. In a linked Danish report, retrograde ejaculation was observed in 9/26 evaluable men with diabetes and 0/16 comparators [40,41]. These measures were unsuitable for a common pooled fertility estimate.

Realized fatherhood reflects reproductive biology alongside opportunities and choices to have children. A German survey observed fewer children and more childlessness than a nonconcurrent background comparator [42]. In men with T1DM, a Finnish cohort reported a lower rate of first live birth (HR 0.77, 95% CI 0.72–0.83) [43], while an international sibling comparison reported a birth-cohort-adjusted offspring-count ratio of 0.91

(95% CI 0.64–0.98, as published) [34]. Certainty was moderate for this evidence body. These outcomes describe realized fertility, not an individual diagnosis of infertility.

Four linked Boeri reports concerned men already attending infertility clinics. Three abstracts included 536 men (58 with prediabetes) and reported non-obstructive azoospermia in 28.1% versus 16.6%; the reported adjusted OR was 2.45 ($p = 0.04$; confidence interval unavailable) [39,44,45]. The 2019 article included 744 men (114 with prediabetes) and reported idiopathic non-obstructive azoospermia in 38/114 versus 81/630 (calculated crude OR 3.39, 95% CI 2.15–5.34) [38]. Its adjusted OR of 1.91 (1.02–3.56) modeled prediabetes as the outcome rather than azoospermia. Because participant overlap could not be resolved, the four reports were linked as MDGS-S08. Evidence certainty was very low, and pregnancy or live birth was not reported.

3.4. During Infertility Care: Use of Surgical Sperm Retrieval

In a matched infertility/ART cohort, surgical sperm retrieval was used in 65/293 couples with paternal T2DM (22.2%) and 57/1169 comparators (4.9%) [31]. The published adjusted OR was 4.80 (95% CI 3.24–7.12; low certainty). This measures procedure use, which is influenced by clinical indications and treatment decisions; it does not directly measure impaired sperm production. The printed crude OR and BMI-stratified event totals differ from calculations based on the overall counts (Appendix S32), so the published adjusted estimate was retained without reconstructing its model.

3.5. Following Transfer or Recognized Pregnancy: Loss and Live Birth

Kasman et al. reported 958,804 pregnancy observations in claims data [25]. Paternal diabetes was associated with ectopic pregnancy (adjusted RR 1.30, 95% CI 1.23–1.38), spontaneous abortion (1.10, 1.07–1.13), and a composite of pregnancy losses termed 'not live birth' (1.08, 1.04–1.13); the stillbirth estimate was imprecise (1.07, 0.96–1.18). These pregnancy-conditioned outcomes do not estimate the probability of live birth from conception attempts. Diabetes-specific denominators were unavailable, so they were not reconstructed from rounded percentages. Claims-based pregnancy recognition was classified as U. Additional metabolic-syndrome analyses were not treated as diabetes-specific sensitivity analyses; residual confounding remains possible.

A Norwegian registry analyzed 703,746 linked singleton offspring records, including fetal losses registered from 16 weeks' gestation [46]. Paternal diabetes was recorded in 4577 observations and absent in 699,169; these are offspring records, not unique fathers. Estimates for late miscarriage at 16–21 weeks (IRR 1.72, 95% CI 0.83–3.54) and stillbirth from 22 weeks (IRR 1.19, 95% CI 0.66–2.14) were imprecise. The diabetes/no-diabetes record counts differ from the model's cardiometabolic-disease-free reference category.

Four ART studies reported pregnancy loss after clinical pregnancy: Wang R, OR 0.96 (95% CI 0.31–2.96) [30]; Liu 2026, OR 1.12 (0.76–1.67) [31]; Liu 2020, OR 2.70 (0.97–7.55) [47]; and Rama Raju, OR 3.07 (0.77–12.19) [48]. Each confidence interval included 1.0. Differences in eligibility, outcome definitions, and repeated observations within couples limited comparability. Figure 3 therefore presents individual estimates; exploratory aggregate calculations appear in Table S20.

Wang L et al. studied 921 first single-blastocyst frozen-thawed transfers across paternal fasting-glucose quartiles: Q1, 3.90–<4.82 mmol/L ($n = 229$); Q2, 4.82–<5.12 ($n = 231$); Q3, 5.12–<5.41 ($n = 233$); and Q4, 5.41–<6.10 [49]. Live birth was observed in 36.0% of Q4 versus 46.7% of Q1 transfers. The unadjusted four-group comparison yielded $p = 0.102$, whereas the adjusted Q4-versus-Q1 OR was 0.64 (95% CI 0.43–0.95). The model included embryo-related covariates potentially measured after paternal exposure. The study defined live birth as delivery after 28 gestational weeks and calculated rates per transfer.

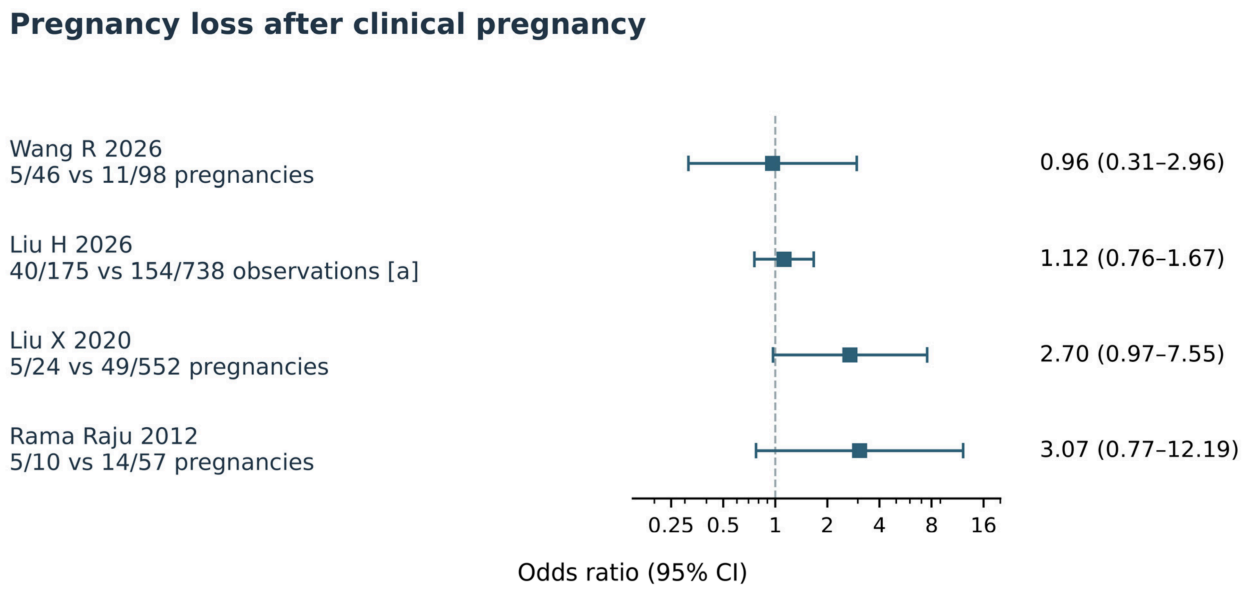


Figure 3. Study-specific pregnancy-loss ORs following clinical pregnancy in paternal-T2DM ART cohorts. Data are from Wang R. et al. [30], Liu H. et al. [31], Liu X. et al. [47], and Rama Raju et al. [48]. Counts for Liu X. et al. [47] were verified as 5/24 versus 49/552. Confidence intervals include the null value in all four studies. No pooled estimate is presented because populations and analytical units differ, including possible repeated observations within couples.

Yang et al. analyzed 370 ultrasound-confirmed singleton pregnancies after frozen-thawed transfer, including 29 with paternal FPG > 6.1 mmol/L and 341 comparators [26]. Live births occurred in 17/29 versus 279/341 (crude OR 0.315, 95% CI 0.143–0.693); miscarriages occurred in 12/29 versus 62/341 (crude OR 3.176, 95% CI 1.444–6.989). The source reported adjusted ORs of 0.635 (0.456–0.884) and 1.575 (1.131–2.195), respectively. However, Tables 3 and 4 of the original study by Yang et al. [26] do not establish whether FPG was modeled as a binary group or continuous predictor. Live birth was defined as delivery after 28 weeks and miscarriage as loss before 28 weeks. The adjusted binary contrast therefore remains uncertain, and the complementary outcomes are not independent evidence.

In the Liu cohort, cumulative live birth was analyzed among completed oocyte-retrieval courses: 124/273 exposed versus 520/1086 comparator courses (45.4% versus 47.9%; adjusted OR 0.81, 95% CI 0.59–1.11; low certainty) [31]. These denominators are narrower than those used for surgical retrieval. Live birth meant the first delivery of at least one infant after 24 weeks per completed course. The 293 men/couples with T2DM were also divided by HbA1c: <7.0% ($n = 29$), 7.0–8.4% ($n = 106$), and >8.4% ($n = 158$). These within-diabetes categories are distinct from fasting-glucose quartiles in other studies and do not define a treatment target.

3.6. Post-Vasectomy TESE–ICSI: Live Birth in Selected Couples

The linked Hervás reports examined different post-vasectomy TESE–ICSI populations [27,28]. In the 2021 autologous-oocyte cohort, live birth per couple after successful sperm retrieval was 41.7% among 12 men with diabetes versus 46.2% among 346 comparators. In the 2025 donor-oocyte cohort, restricted to couples reaching transfer, the corresponding rates were 22.2% among nine versus 62.7% among 110 couples. Figure 4 distinguishes couples, completed stimulation cycles, and transfers. Small exposed groups,

different selection criteria, and potential overlap preclude a direct treatment comparison between reports.

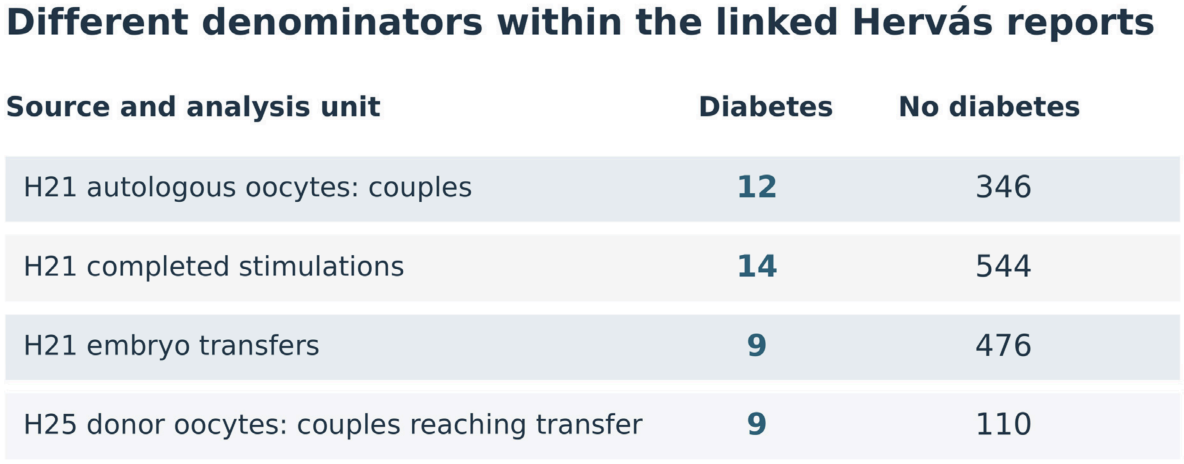


Figure 4. Denominators in the linked Hervás reports. The 2021 autologous-oocyte study reports couples, completed stimulations, and transfers; the 2025 donor-oocyte study reports transfer-conditioned couples. Within each study, paternal diabetes is compared with no diabetes. Results across the two reports are not a treatment contrast.

3.7. Risk of Bias and Certainty

Of the 28 distinct ROBINS-E result-level assessments, 12 were high risk, 11 very high risk, and five raised some concerns; none was low risk. A duplicated result produced 29 rows in the historical assessment file. The 19 GRADE profiles comprised three moderate, eight low, and eight very low ratings. Two Yang moderate ratings concerned published adjusted results with uncertain predictor coding and were not transferred to crude binary contrasts. Assessment details appear in Table S10 and Appendices S24 and S27.

4. Discussion

4.1. What the Different Clinical Estimates Mean

Associations between paternal glycemic exposures and reproductive outcomes arise from different clinical populations. Population studies of T1DM measured realized fatherhood; an infertility-care cohort of T2DM reported retrieval procedures and live birth among completed courses; and fasting-glucose cohorts evaluated outcomes after transfer or confirmed pregnancy [26,31,43,49]. These estimates should inform counseling only within the populations in which they were observed. The principal gap is prognosis for couples at the start of fertility care.

The difference is evident within the Liu cohort: surgical retrieval was analyzed in 293 versus 1169 couples, but cumulative live birth in 273 versus 1086 completed courses [31]. Procedure use is also distinct from underlying sperm production. Similarly, Wang L studied couples reaching transfer, and Yang enrolled confirmed pregnancies [26,49]. Such eligibility restrictions change the patients represented by each estimate and may introduce selection bias [3–5].

Confidence in these associations is limited. Sixteen out of 19 GRADE profiles were low or very low, and none of the 28 distinct ROBINS-E assessments was low risk. Yang's two

archived moderate ratings concern complementary outcomes in the same 370 pregnancies and adjusted models with unresolved predictor coding; they cannot be applied to the crude estimates presented in Table 1 [26]. Heterogeneous analysis units further limit the interpretation of ART pregnancy-loss results. These findings do not establish causality or fertility-specific glycemic treatment targets.

Table 1. Selected clinical associations and their applicability to patients at different entry points.

Clinical Context and Population Entering Analysis	Outcome	Source Association (95% CI)	GRADE	Interpretation for Counseling
Preconception LIFE couples: 14 men with diabetes versus 487 comparators [32]	Time to pregnancy	FOR 0.383 (0.149–0.986)	Low	Relative fecundability; not an individual pregnancy probability
Childhood-onset T1DM population cohort [43]	First live-born child	HR 0.77 (0.72–0.83)	Moderate	Realized fatherhood includes reproductive decisions and access
Liu: 293 versus 1169 infertility-care couples [31]	Surgical sperm retrieval	aOR 4.80 (3.24–7.12)	Low	Procedure use, not measured spermatogenic injury; crude source-count mismatch
Liu: 273 versus 1086 completed treatment courses [31]	Cumulative live birth	aOR 0.81 (0.59–1.11)	Low	Restricted to completed courses; birth after 24 weeks; not initiation prognosis
Wang L: 921 first single-blastocyst transfers [49]	Live birth, FPG Q4 versus Q1	aOR 0.64 (0.43–0.95); 36.0% versus 46.7%	Low	Transfer-conditioned; four-group $p = 0.102$; not a glucose target
Yang: 370 confirmed singleton pregnancies [26]	Live birth after 28 weeks	17/29 versus 279/341; crude OR 0.315 (0.143–0.693)	Not rated †	Selected confirmed pregnancies; source adjusted coding unresolved; archived Moderate does not rate this crude contrast
Four ART studies: clinical pregnancies [30,31,47,48]	Pregnancy loss	ORs 0.96–3.07, reported individually	Very low	Imprecise, distinct populations; no primary pooled estimate
Kasman: 958,804 claims-recognized pregnancy observations [25]	Spontaneous abortion	aRR 1.10 (1.07–1.13)	Low	Pregnancy recognition stage uncertain; not the chance of conceiving

Note: Examples are selected from the 19 evidence bodies detailed in Tables S8 and S14. Each effect estimate applies to its reported population and analysis unit. † For Yang, the table displays a reproducible crude contrast; the archived Moderate rating concerns an adjusted model with unresolved coding and is not assigned to that crude estimate. Birth definitions are compared in Table S30. Abbreviations: ART, assisted reproductive technology; aOR, adjusted odds ratio; aRR, adjusted relative risk; CI, confidence interval; FPG, fasting plasma glucose; FOR, fecundability odds ratio; HR, hazard ratio; OR, odds ratio; T1DM, type 1 diabetes mellitus.

4.2. Contribution Relative to Earlier Reviews and Outcome Standards

Previous reviews considered semen characteristics, sexual and endocrine function, clinical fertility, preconception health, and antidiabetic medications [6–14]. Outcome-methodology studies have emphasized consistent definitions and denominators in infertility research [50–55]. Our synthesis adds a study-level account of the entry criteria, analytic populations, and certainty associated with paternal diabetes and glycemic status. A live-birth estimate after transfer is relevant to couples who reached transfer; it does not answer the corresponding question for everyone initiating treatment.

Live-birth definitions also varied: delivery after 24 weeks in Liu and after 28 weeks in Wang L and Yang, compared with 22 completed weeks in the 2025 international glossary [26,31,49,54]. We retained each source definition (Table S30). The male-infertility core outcome set similarly supports consistent reporting of male, partner, and offspring outcomes [55]. Our S0–S7 labels organize the evidence for clinical interpretation; they are not a validated staging system.

Exposure definitions differed across diabetes diagnoses, within-diabetes HbA1c strata, and fasting-glucose categories [26,31,32,49]. Diabetes duration, medication use, body composition, and timing of glycemic assessment were inconsistently reported. These differences limit comparisons across studies and preclude a unified dose–response estimate or fertility-specific glucose threshold.

Female-partner factors can influence both access to infertility care and reproductive outcomes. Studies addressed these factors through eligibility criteria, matching, or regression, with differing implications for confounding control. Wang R matched female age, BMI, and anti-Müllerian hormone, but did not list partner variables in its published clinical-pregnancy models [30]. Liu used outcome-specific adjustment sets [31], while the Danish ART registry included female-factor and mixed infertility [33]. The available covariates and residual confounding are summarized in Table S17.

4.3. Biological Plausibility Does Not Establish a Clinical Mechanism

Oxidative stress, advanced-glycation products, inflammation, mitochondrial dysfunction, sperm DNA damage, endocrine changes, and erectile or ejaculatory dysfunction offer plausible links between dysglycemia and reproductive health [6–11]. However, the included clinical studies did not test these pathways as mediators of live birth or evaluate whether modifying them improved reproductive outcomes. Mechanistic findings therefore support biological plausibility rather than a demonstrated causal pathway in these cohorts.

Adjustment choices and treatment-stage selection also affect interpretation. LIFE considered characteristics of both partners [32], whereas Liu used outcome-specific adjustment sets [31]. Wang L adjusted for sperm, endometrial, and blastocyst variables that may follow the paternal exposure [49]. Conditioning on transfer or adjusting for post-exposure variables can alter associations. Such estimates may still inform patients at the corresponding stage of care, but they do not describe prognosis at treatment initiation. Covariate details are given in Table S17.

4.4. What Can Be Used in Clinical Counseling

Clinical counseling should begin with the patient's current point in care. LIFE provides a tentative fecundability association for couples attempting conception, based on only 14 men reporting diabetes [32]. Liu describes the use of surgical retrieval during infertility care, not a clinical indication for the procedure, and provides cumulative live-birth data only for completed courses [31]. Wang L, Yang, and Kasman report outcomes conditional on transfer or recognized pregnancy [25,26,49]. Table 1 aligns these estimates with their source populations and certainty. None should be converted directly into an individual's expected chance of live birth from the start of treatment.

4.5. Strengths and Limitations

Linking 24 reports into 19 study families reduced the risk of counting related publications as independent confirmation. Recording study entry, denominators, analytical units, and certainty made the clinical scope of each association explicit. Archived independent screening records and report crosswalks support auditability, although they cannot address bias within the original observational studies.

The underlying studies often had small diabetes-exposed groups, inconsistent exposure and live-birth definitions, limited female-partner information and selection into transfer or pregnancy. Some analyses involved repeated observations within couples or adjustment for potential post-exposure variables (Table S17). The corresponding author authorized an expanded-eligibility pilot on 3 September 2026. During the reported PubMed exercise on 4 September, the team viewed some full texts and numerical results before all authors confirmed the broadened criteria that same day. Although those criteria were subsequently applied to records from all databases, the final scope was not decided without prior exposure to some study findings; possible post hoc selection therefore remains a limitation. The PROSPERO expansion became public on 19 September, and no contemporaneous minutes are available to independently confirm the internal decision sequence. Seven reports remained unretrieved despite documented bibliographic checks and university library assistance; an author of one unretrieved report had not replied. The other six reports date from 1967 to 1990, but age alone does not establish ineligibility. The available abstracts for two of these reports (Table S19b) mainly describe semen or ejaculation-related measurements and do not establish an eligible comparative reproductive-outcome estimate, but neither report was excluded without its full text. The indexed subjects of three other unretrieved reports (Table S19b) may bear directly on male fertility, childlessness or treatment, although their comparative designs and outcomes remain unverified. The absence of these reports may affect the coverage of older male-factor and ejaculatory outcomes, but its direction or magnitude cannot be assessed. Incomplete reviewer-specific final records for some later additions and five forward-citation exclusions recorded only in aggregate are further limitations. The retrieval documentation is provided in Table S19a,b and Appendices S28 and S32.

4.6. Research Needed to Estimate Treatment-Start and Pregnancy-Conditional Outcomes

Future studies should enroll couples before infertility treatment and follow all participants, including those who discontinue care. Live birth should be reported per couple from treatment initiation, alongside conditional outcomes after retrieval, transfer, and pregnancy. Prospective recording of diabetes type, duration, glucose measures, medication, and prognostic factors in both partners would support more credible adjustment. Stable couple identifiers are needed to distinguish individuals from repeated cycles, pregnancies, and offspring [50,54,55]. Whether improving paternal glycemic control changes reproductive outcomes requires appropriately designed intervention studies.

5. Conclusions

Associations between paternal diabetes or glycemic status and reproductive outcomes differ across conception attempts, infertility care, transfer, and pregnancy. Population studies inform fecundability and realized fatherhood; treatment cohorts describe procedure use and outcomes among selected patients; and transfer- or pregnancy-based studies provide stage-conditional estimates. Most evidence remains uncertain, with 16 of the 19 GRADE profiles rated low or very low. Clinical interpretation should reflect the source population and denominator. Current evidence does not establish an individualized live-birth prognosis from treatment initiation or a fertility-specific glucose target. This evidence gap does not diminish the established importance of diabetes management for general health.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/life16111950/s1. Supplementary Material S1 (.docx) contains Tables S1–S20 (including S8a, S19a and S19b) and Table S30; Appendices S1, S2 and S21–S33; and Supplementary Figures S1 and S2. The historical ROBINS-E graphic previously designated Figure S1b was withdrawn in favor of Table S10, and the historical Figure S3 was superseded by main Figure 2. The supplement documents the searches, protocol amendments, study selection, linked

reports, risk-of-bias and GRADE records, outcome definitions, and numerical checks. Supplementary Data S1 (.xlsx) contains study-family registers, denominators, exposure definitions, partner factors, appraisal records, and numerical diagnostics. The PRISMA 2020 and PRISMA-S reporting checklists are provided in the separate file PRISMA2020_PRISMA_S_Checklist.xlsx. Bibliographic identifiers for unavailable reports in the supplementary retrieval register document unresolved eligibility rather than additional included evidence. The full-text-excluded report records in Supplementary Table S12 are indexed in the main bibliography [56–84] solely for screening transparency; none contributes to the 24 included reports or 19 study families. Additional exclusion records from Supplementary Table S13 are cross-referenced as [85–89], and the seven unretrieved records in Supplementary Tables S19a and S19b are indexed as [90–96]. The S12 and S13 reports were excluded; eligibility for the seven unretrieved S19 reports remains unresolved. None was counted among the included studies.

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Abbreviations

ART, assisted reproductive technology; CET, cryo-thawed embryo transfer; CI, confidence interval; CLBR, cumulative live birth rate; FBG, fasting blood glucose; FET, frozen-thawed embryo transfer; FPG, fasting plasma glucose; FOR, fecundability odds ratio; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; ICSI, intracytoplasmic sperm injection; IRR, incidence rate ratio; IVF, in vitro fertilization; JBI, Joanna Briggs Institute; OR, odds ratio; PRESS, Peer Review of Electronic Search Strategies; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR, risk ratio; ROBINS-E, Risk Of Bias In Non-randomized Studies—of Exposures; SWiM, Synthesis Without Meta-analysis; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TESE, testicular sperm extraction.

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