

Clinical evidence and recommendation on the use of Type-2 Diabetes Mellitus drugs in Lactation

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1. Background & Objective

- **500 million adults** worldwide have T2DM (1)
- **>90% of medications** used "off-label" in lactation (2)
- **Only 10%** of approved drugs have lactation data (2)
- **WHO recommends** exclusive breastfeeding for 6 months (3)

OBJECTIVE: Evaluate the available pharmacokinetic data on the plasma-to-breastmilk transfer of first- and second-line T2DM drugs against available clinical guideline recommendations.

2. Methods

Study Design: Systematic review (PROSPERO: CRD42024584391)

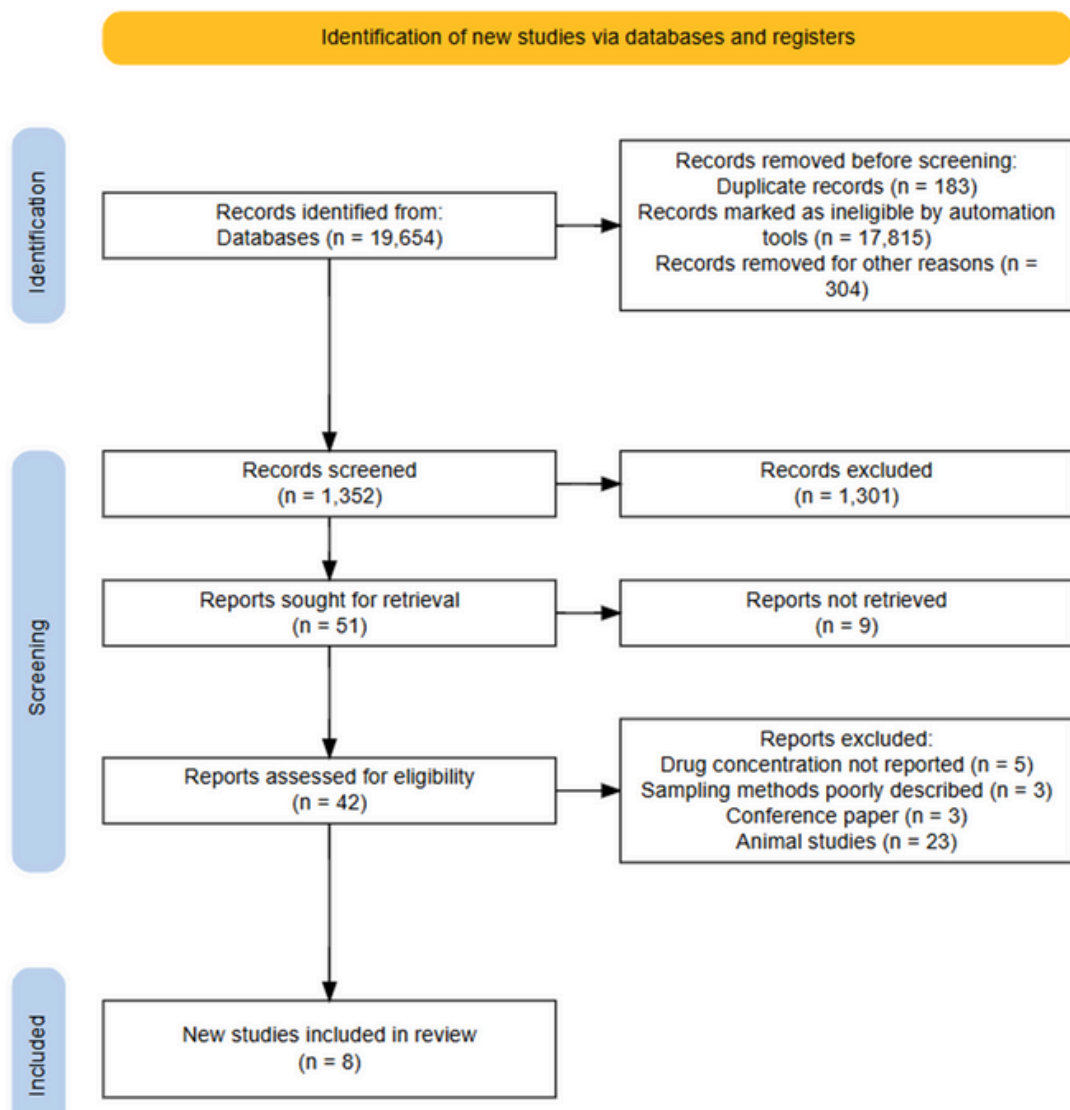
Drug Selection: 20 first/second-line T2DM drugs from:

- American Diabetes Association (ADA)
- National Institute for Health and Care Excellence (NICE)
- American Academy of Clinical Endocrinology (AACE)
- Uganda Clinical Guidelines (UCG)

Search Strategy:

- Databases: PubMed, Scopus, Google Scholar, LactMed®
- Search terms: (Drug) AND (plasma/serum) AND (breast milk) AND (lactation) AND (pharmacokinetics)
- Time: Until March 2025
- Language: English only

Quality Assessment: ClinPK checklist



3b. Results: Study Analysis

Search Results:

- 19,654 articles retrieved
- 1,352 eligible for abstract screening
- 51 full-text articles reviewed
- **8 studies included (1967-2025)**

Study Quality (ClinPK scores):

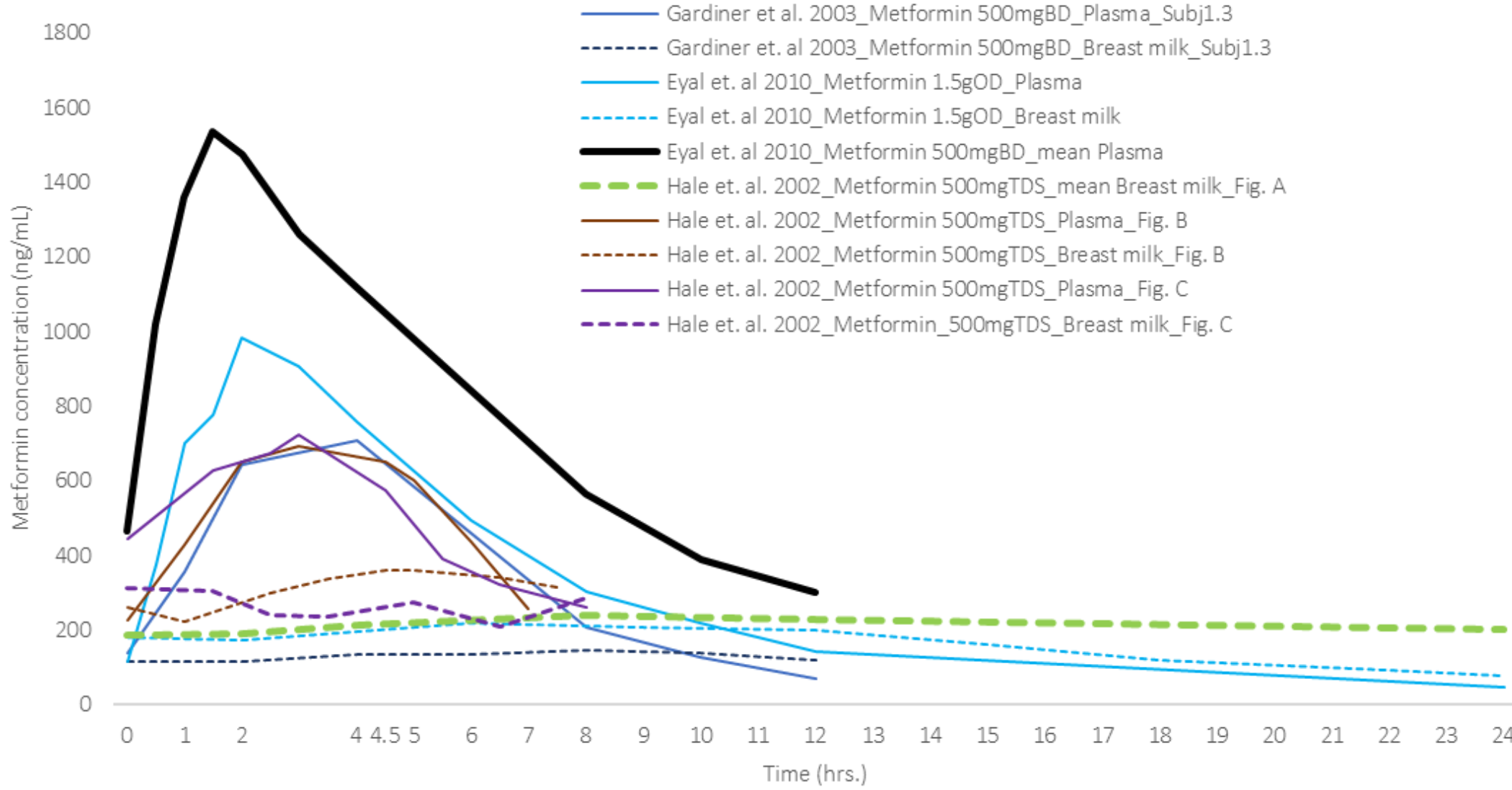
- Range: 45-81%
- Most metformin studies: $\geq 66\%$
- Key limitations: Small sample sizes, methodological variability

Only 5/20 drugs have clinical data:

- **Metformin** (5 studies) – M:P ratio <1 , "safe"
- **Glyburide** – Undetectable in breast milk
- **Glipizide** – Undetectable in breast milk
- **Tolbutamide** – Detectable in breast milk
- **Semaglutide** – Undetectable in breast milk

Metformin Key Results:

- M:P ratio: 0.34-0.63
- Relative Infant Dose: 0.11-0.65%
- No adverse effects in infants
- Considered "safe" for lactation



Metformin plasma (solid lines) and breast milk (dashed lines) concentration-time profiles under steady-state conditions after multiple doses across five clinical studies. Thin lines: individual profiles and thick lines: Mean profiles obtained from several individuals. Data was digitized from the publications using WebPlotDigitizer (Version 4.7).

3a. Results: Clinical Guideline Analysis

180 recommendations assessed across 9 sources:

- 51.7% provided explicit guidance
- **78% recommended AGAINST** use during breastfeeding
- Only **4.4% based on human studies**
- 48.3% were "silent" on drug use

Drug	NICE/NP	PLMBO	Scopus	LactMed	JAMA	LOTIS	RAACGP	NICE London	WHO
BIGUANIDES									
Metformin	Y	R	R	Y	Y	Y	—	Y	N
SULFONYLUREAS									
Glyburide	—	R	R	Y	—	A	—	—	N
Glipizide	—	I	N	A	—	A	—	—	N
Tolbutamide	—	N	N	A	—	N	—	—	N
Glimepiride	—	N	N	N	—	N	—	N	N
Gliclazide	—	N	N	N	—	N	—	N	N
GLP-1 RECEPTOR AGONISTS									
Semaglutide	—	N	N	—	—	N	—	—	—
Liraglutide	—	N	N	N	—	N	—	—	—
SGLT2 INHIBITORS									
Empagliflozin	—	N	N	N	—	N	—	—	—
Dapagliflozin	—	N	N	N	—	N	—	—	—
DPP-4 INHIBITORS									
Sitagliptin	—	N	N	N	—	N	—	—	—
THIAZOLIDINEDIONES									
Pioglitazone	—	R	R	N	—	N	—	—	—

Y - Recommended N - Not Recommended R - Risk/Benefit Decision A - Alternative Suggested — - Silent (No Guidance) I - Inconclusive Evidence

5. Evidence Gaps & Clinical Implications

Major Limitations:

- **75% of T2DM drugs** lack any lactation data
- **15/20 drugs** have NO transfer studies
- Inconsistent study methodologies
- Limited infant safety data
- Variable sampling strategies

Novel Drugs with NO Data:

- SGLT2 inhibitors (Empagliflozin, Dapagliflozin)
- Most GLP-1 RAs (Liraglutide, Exenatide, Tirzepatide)
- DPP4 inhibitors

Current Challenges:

- **Contradictory guideline recommendations**
- Lack of evidence-based guidance
- Potential for early breastfeeding cessation
- **"Off-label" use for all T2DM medications**

Safety Considerations:

- Most recommendations based on **"unknown risk"**
- Theoretical calculations often **inaccurate**
- Need for individualized risk-benefit assessment

6. Conclusions

Key Messages:

1. **Critical evidence gap:** Only 25% of T2DM drugs have lactation transfer data
2. **Inconsistent guidance:** Clinical recommendations largely unsupported by human studies
3. **Safe options exist:** Metformin appears safe based on multiple studies
4. **Newer drugs understudied:** No data for widely-used SGLT2-i or most GLP-1 RAs

Future Research Priorities:

- Conduct lactation studies for newer T2DM medications
- Standardize study methodologies following FDA guidance
- Implement physiologically-based pharmacokinetic (PBPK) modeling
- Develop evidence-based clinical consensus guidelines

Study Limitations

- English-language publications only
- Limited to published studies
- Variable study quality and methodology
- Small sample sizes in included studies

References

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