Hemoglobin A1c (HbA1c) as a Novel Biomarker of Embryo Competence and Pregnancy Success in Non-Diabetic Single Frozen Embryo Transfer (sFET) Cycles

Ontario Network of Experts in Fertility
life through knowledge

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INTRODUCTION

- Peri-conception hyperglycemia—even below the diabetic threshold—may impair oocyte and embryonic development through mitochondrial dysfunction, oxidative stress, and altered cellular metabolism.
- HbA1c, a marker of average glycemia over ~3 months, is associated with adverse obstetric outcomes in non-diabetic women.
- Whether HbA1c predicts embryo competence and pregnancy success in IVF remains unknown.

OBJECTIVE:
To evaluate whether HbA1c prior to oocyte retrieval predicts embryo competence and clinical pregnancy rate (CPR) in non-diabetic women undergoing single frozen embryo transfer (sFET).

METHODS

DESIGN
Retrospective cohort study.

STUDY POPULATION
321 sFET cycles from non-diabetic women (HbA1c <6.5%) at ONE Fertility, Burlington, Ontario, between January 1, 2024 and December 31, 2025.

EXPOSURE
Pre-retrieval HbA1c (%), drawn a median of 4.0 months prior to oocyte retrieval.

SAMPLE SIZE
321 total cycles, 280 with complete blastocyst data, 177 with available top-quality embryo (TQE) data, and 147 transfer cycles for CPR analysis.

OUTCOMES
- Primary embryo outcomes: Blastocyst count (BC), Blastocyst-to-fertilized oocyte ratio (BFOR), Top-quality embryo count (TQE; ≥2BB by Gardner's criteria)
- Clinical outcome: Clinical pregnancy rate (CPR) per transfer

STATISTICAL ANALYSIS
Linear regression assessed HbA1c as a predictor of BC, BFOR, and TQE, controlling for patient age, BMI, AMH, ovulatory PCOS status, and total gonadotropin dose. Blastocyst models additionally adjusted for oocytes retrieved as a covariate. Logistic regression modeled CPR as a function of HbA1c, BMI, and patient age. Each outcome was also compared in an HbA1c-inclusive model against a baseline model without HbA1c. Significance was set at p<0.05.

KEY COVARIATES
Age | BMI | AMH | PCOS (yes/no) | Total gonadotropin dose (IU) | Oocytes retrieved*

EXCLUSIONS
- Incomplete data (n=29)
- No embryo transfer (n=13)

DEFINITIONS
- Top-quality embryo (TQE): ≥2BB by Gardner's grading system
- Clinical pregnancy: presence of a gestational sac with fetal heartbeat

*Adjusted for in blastocyst outcome models.

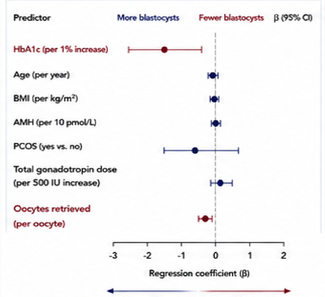
RESULTS

PRIMARY EMBRYO OUTCOMES

1. BLASTOCYST COUNT (BC)

Higher pre-retrieval HbA1c is independently associated with fewer blastocysts

Adjusted association with blastocyst count
Linear regression model (N = 280)



Multivariable Linear Regression Model for Blastocyst Count (N = 280)

Predictor	β (95% CI)	p-value
HbA1c (per 1% increase)	-1.44 (-2.60, -0.28)	0.014
Age (per year)	-0.06 (-0.15, 0.02)	0.15
BMI (per kg/m²)	-0.03 (-0.09, 0.03)	0.33
AMH (per 10 pmol/L)	0.01 (-0.06, 0.08)	0.79
PCOS (yes vs. no)	-0.46 (-1.36, 0.45)	0.32
Total gonadotropin dose (per 500 IU increase)	0.05 (-0.16, 0.26)	0.64
Oocytes retrieved (per oocyte)	-0.18 (-0.34, -0.03)	0.019

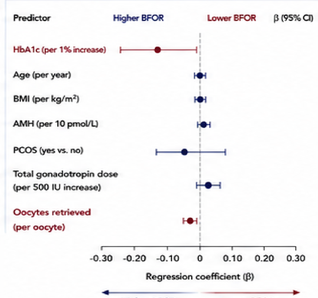
KEY FINDING
β = -1.44
blastocysts per 1% increase in HbA1c
95% CI -2.60 to -0.28 *p* = 0.014

≈1 fewer blastocyst for every 0.7% increase in HbA1c

2. BLASTOCYST FORMATION RATE (BFOR)

Higher pre-retrieval HbA1c is independently associated with lower blastocyst formation efficiency

Adjusted association with BFOR (BC / 2PN)
Linear regression model (N = 280)



Multivariable Linear Regression Model for BFOR (BC / 2PN) (N = 280)

Predictor	β (95% CI)	p-value
HbA1c (per 1% increase)	-0.131 (-0.260, -0.003)	0.045
Age (per year)	-0.004 (-0.014, 0.007)	0.48
BMI (per kg/m²)	-0.005 (-0.014, 0.004)	0.25
AMH (per 10 pmol/L)	0.006 (-0.002, 0.014)	0.13
PCOS (yes vs. no)	-0.028 (-0.106, 0.050)	0.48
Total gonadotropin dose (per 500 IU increase)	0.006 (-0.010, 0.022)	0.48
Oocytes retrieved (per oocyte)	-0.018 (-0.031, -0.005)	0.008

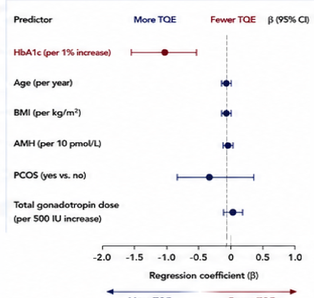
KEY FINDING
β = -0.131
BFOR (BC/2PN) per 1% increase in HbA1c
95% CI -0.260 to -0.003 *p* = 0.045

Lower blastocyst formation rate with increasing HbA1c

3. TOP-QUALITY EMBRYO COUNT (TQE)

Higher pre-retrieval HbA1c is independently associated with fewer top-quality embryos

Adjusted association with TQE count
Linear regression model (N = 177)



Multivariable Linear Regression Model for TQE Count (N = 177)

Predictor	β (95% CI)	p-value
HbA1c (per 1% increase)	-1.02 (-1.49, -0.54)	<0.001
Age (per year)	-0.02 (-0.06, 0.02)	0.22
BMI (per kg/m²)	-0.02 (-0.05, 0.02)	0.37
AMH (per 10 pmol/L)	0.00 (-0.03, 0.04)	0.86
PCOS (yes vs. no)	-0.22 (-0.67, 0.23)	0.34
Total gonadotropin dose (per 500 IU increase)	0.04 (-0.06, 0.13)	0.45

KEY FINDING
β = -1.02
top-quality embryo offspring (TQE) per 1% increase in HbA1c
95% CI -1.49 to -0.54 *p* < 0.001

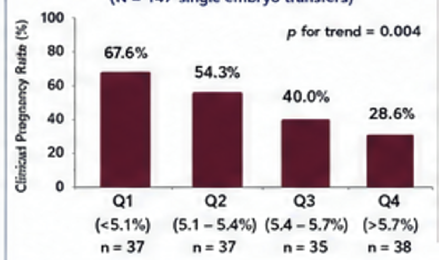
~1 fewer top-quality embryo for every 0.5% increase in HbA1c

Higher pre-retrieval HbA1c is independently associated with poorer embryo outcomes.
~1 fewer blastocyst for every 0.7% increase in HbA1c (p = 0.014) • Lower BFOR (p = 0.045) • ~1 fewer TQE for every 0.5% increase in HbA1c (p < 0.001)

All models adjusted for age, BMI, AMH, PCOS status, total gonadotropin dose, and oocytes retrieved.
BC: blastocyst count; BFOR: blastocyst formation rate (BC/2PN); TQE: top-quality embryo count.

CLINICAL OUTCOME – CLINICAL PREGNANCY RATE (CPR)

Clinical pregnancy rate by HbA1c quartile
(N = 147 single embryo transfers)



Multivariable Logistic Regression (for CPR)

	Adjusted OR (95% CI)	p-value
HbA1c (per 1% increase)	0.16 (0.03 – 0.90)	0.032
Age (per year)	0.96 (0.88 – 1.06)	0.40
BMI (per kg/m²)	0.96 (0.88 – 1.04)	0.28
AMH (per 10 pmol/L)	1.02 (0.94 – 1.11)	0.62
Ovulatory PCOS (yes vs. no)	0.89 (0.28 – 2.82)	0.83
Total gonadotropin dose (per 500 IU increase)	1.01 (0.77 – 1.32)	0.94

Each 1% increase in HbA1c was associated with an 84% lower odds of clinical pregnancy (adjusted OR 0.16, 95% CI 0.03–0.90, *p* = 0.032).

KEY FINDINGS

Higher HbA1c, even within the non-diabetic range (<6.5%), was independently associated with poorer embryo competence, including fewer blastocysts, lower blastocyst formation rate, and fewer top-quality embryos.

Higher HbA1c was independently associated with lower odds of clinical pregnancy after single frozen embryo transfer.

A graded decline in clinical pregnancy rate was observed across HbA1c quartiles (p for trend = 0.004).

These associations persisted after adjustment for key patient characteristics and ovarian response markers, including age, BMI, AMH, PCOS status, and total gonadotropin dose.

HbA1c may serve as a novel, modifiable biomarker of embryo competence and reproductive success in IVF/sFET cycles, even below the diabetic threshold.

LIMITATIONS

- Retrospective, single-center study.
- Residual confounding by unmeasured factors (e.g., diet, physical activity, insulin resistance).
- Findings require validation in prospective and multi-center cohorts.

CONCLUSION

In non-diabetic women undergoing IVF/sFET, higher pre-retrieval HbA1c—even within the non-diabetic range—is independently associated with reduced embryo competence and lower clinical pregnancy rates. These results suggest that subtle differences in glycemic exposure may influence early embryonic development and highlight the potential role of HbA1c as a clinically applicable biomarker to optimize reproductive outcomes.

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