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Health Economics

Cost effectiveness of early metformin in addition to usual care in the reduction of gestational diabetes mellitus effects (EMERGE)—A randomised placebo-controlled clinical trial

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Abstract

Aims: To investigate the cost-effectiveness of early initiation of metformin and usual care for gestational diabetes mellitus (GDM).

Methods: Economic evaluation from a healthcare perspective, based on the EMERGE randomised controlled trial. In total, 535 women with GDM were randomised to placebo in addition to usual care or metformin in addition to usual care. Economic outcomes included incremental healthcare costs and quality adjusted life years (QALYs) and expected cost-effectiveness at cost-effectiveness threshold values of €20,000, €45,000 and €100,000 per QALY gained. Uncertainty was explored using parametric, non-parametric, deterministic and probabilistic methods and heterogeneity using subgroup analysis.

Results: On average, relative to the placebo arm, the early metformin arm was associated with non-statistically significant mean increases of €193.07 (95% CI: −€789.88, €1176.01; $p = 0.700$) and 0.002 QALYs (95% CI: −0.009, 0.013; $p = 0.771$). In terms of expected cost-effectiveness at threshold values of €20,000, €45,000 and €100,000 per QALY gained, the probability of the early metformin arm being more cost-effective was estimated at 0.423, 0.452 and 0.524. Exploratory subgroup analyses provided more favourable but not definitive evidence in favour of the early metformin arm for cohorts with previous GDM and previous caesarean section.

Conclusions: We do not find definitive evidence that early initiation of metformin in addition to usual care for GDM was more cost-effective than usual care alone. The clinical and economic evidence may be considered equivocal, but worthy of further examination.

Trial Registration: EudraCT Number 2016-001644-19; NCT NCT02980276; https://clinicaltrials.gov/ct2/show/NCT02980276.

KEYWORDS
cost-effectiveness, gestational diabetes mellitus, metformin

1 | INTRODUCTION

Gestational diabetes mellitus (GDM), defined as carbohydrate intolerance resulting in hyperglycaemia with onset during pregnancy,[1] is a global health problem.[2] GDM is associated with increased risks of adverse maternal outcomes and adverse foetal outcomes,[3,4] and increased healthcare utilisation and costs.[5,6] Moreover, both women and infants are at increased long-term risk of developing type 2 diabetes mellitus.[7–9]

While improved glycaemic control is associated with improved maternal and foetal outcomes,[10,11] there is uncertainty about the optimal management approach following GDM diagnosis. Current clinical guidelines recommend an initial strategy of medical nutritional therapy and exercise, with pharmacotherapy reserved for those who fail to achieve glycaemic control after lifestyle management.[12] Insulin is considered first-line pharmacotherapy effective in achieving glycaemic control and improving several maternal and perinatal outcomes.[13,14] However, insulin is also associated with multiple adverse outcomes, including increased rates of maternal and infant hypoglycaemia, excess gestational weight gain, higher rates of caesarean birth and neonatal intensive care unit admission.[13,14]

Recent evidence on the safety of metformin in pregnancy supports its emergence as an alternative therapeutic approach to insulin for the management of GDM.[15,16] Compared to insulin, metformin is reported to be associated with improved maternal and foetal metabolic outcomes for GDM.[15] However, concerns exist about higher rates of spontaneous pre-term birth[15,16] and small for gestational age outcomes.[17] Importantly, these data reflect current clinical practice, where metformin is only prescribed when there is a failure to achieve glycaemic control with lifestyle modification. An alternative approach involves the early initiation of metformin at GDM diagnosis, with goals of improved glycaemic control, reduced need for insulin therapy and other clinical advantages beyond glycaemic control.[18]

The EMERGE randomised controlled trial (RCT) tested the hypothesis that early metformin was associated with superior GDM outcomes.[19,20] Although the trial reported that early metformin in addition to usual care was not superior for the composite primary outcome (insulin initiation or a fasting laboratory glucose value ≥5.1 mmol/L at either week 32 or 38 of gestation (risk ratio (RR), 0.89; 95% CI: 0.78–1.02; $p = 0.13$)), it demonstrated positive and statistically significant impacts on multiple secondary maternal and foetal outcomes.[20] Further, although the trial was not primarily designed to assess safety, it did provide reassurance that early metformin does not increase the risk of adverse events in mothers or infants.[20]

In addition to the evidence on the safety and clinical effectiveness, decisions regarding the adoption of health technologies in clinical practice should depend upon their expected cost-effectiveness.[21] This article reports on the cost-effectiveness of early metformin in addition to usual care for GDM based on the EMERGE RCT.

What's new?

What Is Already Known

- Early initiation of metformin for Gestational Diabetes Mellitus appears to be safe and effective; however, little is known about its cost-effectiveness.

What Study Has Found

- In this health economic evaluation based on a randomised controlled trial, we did not find definitive evidence that early initiation of metformin for GDM is more cost-effective than usual care.

Implications

- Further research is required to provide clinical and economic evidence on early metformin for GDM.

2 | METHODS

2.1 | Overview

The study was conducted following the guidelines for the conduct of economic evaluation in Ireland,[22] and reported in line with international standards.[23] The costing perspective of the healthcare provider (the Irish Health Service Executive) was adopted, and health outcomes were expressed using quality-adjusted life years (QALYs). The mode of analysis was a trial-based evaluation with a

time horizon of the trial follow-up period: recruitment to 12 weeks post-delivery. Neither costs nor outcomes were discounted. The analysis was conducted on an intention-to-treat basis using complete case data. Given the level and pattern of missing data, we proceeded with the assumption that data were missing at random, and imputation methods were not employed. Uncertainty was addressed using statistical inference methods, in the form of 95% confidence intervals and hypothesis tests, probabilistic sensitivity analysis, reported in the form of estimated probabilities that the early metformin intervention was more cost-effective at a range of potential threshold values (λ) that the healthcare system may be willing to pay per additional QALY gained,[21] and deterministic sensitivity analysis. All analyses were undertaken using Stata 15 and Microsoft Excel statistical software packages.

2.2 | Randomised controlled trial (RCT)

Full details on the RCT are described elsewhere.[19,20] In brief, EMERGE was a phase III, parallel, superiority, randomized, double-blind, placebo-controlled trial, conducted in line with best practice.[24] Ethical approval was granted by the Clinical Research Ethics Committee of Galway University Hospital (2016-001644-19). Eligible participants were women aged 18–50 years diagnosed with GDM according to World Health Organisation (WHO) 2013 criteria.[1] Exclusion criteria included an established diagnosis of diabetes (type 1, type 2, monogenic or secondary), a fasting glucose ≥7 mmol/L or a 2 h value ≥11.1 mmol/L on the oral glucose-tolerance test (75 g OGTT) or a known intolerance to metformin. Between June 2017 and September 2022, 535 pregnancies (in 510 women) were recruited and underwent randomization; 268 to metformin and 267 to placebo. Data on 526 (98%) pregnancies were available for analysis at follow-up. Participants were recruited at variable lengths of gestation and had variable durations of treatment exposure and follow-up.

Metformin or matched placebo was started at 500 mg daily and titrated upwards every 2 days over 10 days to a maximum of 2500 mg daily and taken until the birth of the baby. Usual care consisted of standardised advice on medical nutritional therapy and exercise, in addition to the standard antenatal, delivery and postnatal care pathway. Participants performed 7-point glucose testing at meal time (before and 1 h after) and before bed and attended at 2–4 weekly intervals at an antenatal/diabetes clinic. Insulin was started if two or more home glucose readings were outside the pre-specified glucose targets (fasting ≤5 mmol/L, 1-h post-prandial ≤7 mmol/L) at any clinic visit. If insulin was initiated, standard clinical guidelines were followed, and study medication was continued.

2.3 | Cost analysis

Four cost components were included and expressed in Euros (€) in 2022 prices. Unit cost estimates for each activity (see Table 1) were based on national data sources and, where necessary, were transformed to Euros (€) in 2022 prices using appropriate indices.[22,25]

The first cost component related to the resources expended in delivering *GDM Care*, including the combined costs of 75-g oral glucose-tolerance tests, lifestyle advice consultations, metformin, insulin, laboratory tests and blood glucose monitoring. The second cost component related to *Antenatal Care*, including the combined costs of ultrasound scans, outpatient clinic visits, inpatient nights and day cases, accident and emergency department visits and general practice visits. The third cost component related to *Delivery Care*, including the combined costs of mode of delivery, maternal length of stay and neonatal intensive care unit admission. The fourth cost component related to *Postnatal Care* and included ultrasound scans, outpatient clinic visits, inpatient nights and day cases, accident and emergency department visits, general practice visits and neonatal intensive care unit admissions in the 12 weeks post-delivery.

Resource use data was recorded prospectively by the study research team. A vector of unit costs was applied to calculate the cost associated with each resource activity. For the incremental analysis, a '*total healthcare cost*' variable was constructed by aggregating individual resource costs over the follow-up period. For the statistical analysis, the estimation of the incremental cost was undertaken using a generalized linear model (GLM) regression. The multivariable regression was estimated controlling for the treatment arm and a set of clinical and socioeconomic covariates: age, ethnicity, first pregnancy status, previous caesarean section status, previous GDM status, medical condition status, smoking status, body mass index at screening, employment status, educational attainment status, marital status, medical card status, private health insurance status, private consultant status and gestational age at screening. To account for the distributional nature of the cost data, an Inverse Gaussian variance function and log link function were assumed. The choice of distribution was informed by a Modified Park test, and the link function was informed by a Pearson correlation test, a Pregibon link test and a Modified Hosmer and Lemeshow test.[21]

2.4 | Health outcome analysis

Health outcomes were expressed in terms of QALYs gained over the trial follow-up period, calculated based on

TABLE 1 Unit cost data in 2022 € prices.

Resource category	Resource item	Unit cost	Source of estimates
GDM care	75-g Oral Glucose-Tolerance Test (OGTT)	€46.27	Gillespie et al. (2011)
	Lifestyle (Diet and Exercise) Advice Consultations	€244.16	Gillespie et al. (2011)
	Metformin Per 500 mg Tablet	€0.02	Primary Care Reimbursement Service (PCRS)
	Insulin—Fast Acting Per Unit	€0.28	Primary Care Reimbursement Service (PCRS)
	Insulin—Intermediate Acting Per Unit	€0.28	Primary Care Reimbursement Service (PCRS)
	Insulin—Long Acting Per Unit	€0.52	Primary Care Reimbursement Service (PCRS)
	Pharmacy Dispensing Free	€5.48	Health Information and Quality Authority (HIQA)
	Laboratory Testing—Per Set	€75.00	Study Records—Market Quote
	Blood Glucose Monitoring Per Week	€14.85	Health Information and Quality Authority (HIQA)
Antenatal care	Ultrasound Scans	€202.12	Study Records—Market Quote
	Hospital Outpatient (OPD) Clinic Visits	€194.88	Hospital Pricing Office (HPO)
	Hospital Inpatient Nights	€988.00	Hospital Pricing Office (HPO)
	Hospital Day Cases	€767.00	Hospital Pricing Office (HPO)
	Accident and Emergency Visits	€332.26	Hospital Pricing Office (HPO)
	General Practice Visits	€57.51	Smith et al. (2021)
Delivery care	Normal Vaginal Delivery	€2547.28	Hospital Pricing Office (HPO)
	Instrumental/Assisted Vaginal Delivery	€3714.85	Hospital Pricing Office (HPO)
	Elective Caesarean Section Delivery	€3855.31	Hospital Pricing Office (HPO)
	Emergency Caesarean Section Delivery	€6009.89	Hospital Pricing Office (HPO)
	Neonatal Intensive Care Unit Per Admission	€8768.18	Hospital Pricing Office (HPO)
	Neonatal Intensive Care Unit Per Night	€1155.93	Hospital Pricing Office (HPO)
Postnatal care	Ultrasound Scans	€202.12	Study Records—Market Quote
	Hospital Outpatient (OPD) Clinic Visits	€194.88	Hospital Pricing Office (HPO)
	Hospital Inpatient Nights	€988.00	Hospital Pricing Office (HPO)
	Hospital Day Cases	€767.00	Hospital Pricing Office (HPO)
	Hospital Accident and Emergency Department Visits	€332.26	Hospital Pricing Office (HPO)
	General Practice Visits	€57.51	Smith et al. (2021)
	Neonatal Intensive Care Unit Per Admission	€8768.18	Hospital Pricing Office (HPO)

Note: Unit costs were transformed and inflated to 2022 Euro prices following Irish guidance using health inflation indices and purchasing power parity indices.

participant responses to the EuroQol[26] EQ-5D-5L instrument, collected via patient questionnaire at baseline and follow-up. In completing the EQ-5D-5L, an individual is located in one of 3125 health states, each of which may be transformed into a health state index score using values elicited from the general population. The EQ-5D-5L value set scoring algorithm for Ireland was adopted,[27] and QALYs gained over the trial follow-up period were calculated using the area under the curve method.[21] For the incremental analysis, a '*QALYs gained*' variable was constructed using EQ-5D-5L index scores at baseline, 4 and 12 weeks post-partum. Estimation of incremental QALYs gained was undertaken using a GLM regression model assuming a Gaussian variance function and an identity link function. In addition to the covariates listed above for the cost analysis, the baseline EQ-5D-5L utility score was included as a covariate in the QALYs regression as per methodological guidance.[21]

2.5 | Expected cost-effectiveness analysis

To explore expected cost-effectiveness, probabilistic analysis was conducted and presented using cost-effectiveness acceptability curves, which incorporated both the joint sampling uncertainty around the mean cost-effectiveness estimates and the uncertainty around the true cost-effectiveness threshold value.[21] In the Irish context, cost-effectiveness thresholds in the range of €20,000–€45,000 per QALY have been employed for decision-making,[22] although lower and higher values may apply in certain contexts. The probabilistic analysis was conducted using a non-parametric bootstrapping technique, employing 1000 replications and enabled the generation of cost-effectiveness probabilities for threshold values of €20,000, €45,000 and €100,000.

2.6 | Deterministic sensitivity analysis and exploratory subgroup analysis

Deterministic analyses were conducted to test the robustness of the base-case results to variations in the methods and assumptions employed. Subgroup analyses, which were clinically informed but not pre-specified, explored heterogeneity.

3 | RESULTS

Results are presented in Tables 2–4 and in the appendix. Descriptive statistics for baseline maternal characteristics were similar for the early metformin and placebo control arms (Table 2). Complete case data available for analysis was 88% for the intervention arm and 89% for the placebo arm for the total cost variable, and 81% for the intervention arm and 83% for the placebo arm for the QALYs variable (see Appendix Table A1).

Descriptive statistics for EQ-5D-5L index scores, QALYs gained, healthcare resource use and costs are summarised in Table 3. Descriptive data for the EQ-5D-5L dimensions are presented in Appendix Table A2. Mean QALYs gained was 0.468 (SD: 0.041) in the metformin arm and 0.465 (SD: 0.044) in the placebo arm, and mean total healthcare cost was €11947.54 (SD: 8232.03) in the intervention arm and €11321.50 (SD: 5567.93) in the placebo arm.

The results from the incremental cost-effectiveness analyses are presented in Table 4. In the base-case analysis, the early metformin arm was associated with non-statistically significant mean increases of €193.07 (95% CI: −€789.88, €1176.01; $p=0.700$) and 0.002 QALYs gained (95% CI: −0.009, 0.013; $p=0.771$). In terms of expected cost-effectiveness at threshold values of €20,000, €45,000 and €100,000 per QALY gained, the probability of the early metformin arm being more cost-effective was estimated at 0.423, 0.452 and 0.524, respectively.

The results from sensitivity analyses are presented in Table 4, and generally confirm the findings from the base-case analysis, with the probability of the early metformin arm being cost-effective failing to rise above 0.550 at the €20,000 and €45,000 thresholds in the scenarios explored. The exception was the sensitivity analysis which focused on the total GDM care cost only subcategory. These results reveal the contribution of the uncertainty surrounding the incremental cost estimates for Antenatal, Delivery and Postnatal care to the overall uncertainty in the cost-effectiveness results. The results are explored further in Appendix Table A3. In particular, the early metformin intervention arm was associated with an increase in metformin costs of €34.95 (95% CI: €34.52, €35.37; $p<0.001$), and a reduction in insulin costs of €192.53 (95% CI: −€275.50, −€109.56; $p<0.001$). However, early metformin was associated with non-statistically significant increases in the costs of Antenatal Care (€44.33: 95% CI: −€566.74, €655.40; $p=0.8867$), Delivery Care (€439.21: 95% CI: −€593.37, €1471.79; $p=0.4038$) and Postnatal Care (€173.20: 95% CI: −€344.63, €691.04; $p=0.5113$).

The results from exploratory subgroup analyses are presented in Table 4 and Appendix Table A4. In the cohort with previous GDM, expected cost-effectiveness was 0.661 and 0.716 at the €20,000 and €45,000 thresholds respectively. In the previous caesarean section cohort, the expected cost-effectiveness of early metformin was 0.863 and 0.799 at the €20,000 and €45,000 thresholds respectively.

The results from a cost-effectiveness analysis which focused on the primary composite clinical outcome measure rather than QALYs indicated that if decision-makers were willing to pay €500 or more to prevent an additional adverse outcome, there would be an over 90% probability of the early metformin arm being more cost-effective than usual care (see Appendix Table A5).

4 | DISCUSSION

This study evaluated the cost-effectiveness from a healthcare perspective of early initiation of metformin at the time of diagnosis in addition to usual GDM care, based on the EMERGE RCT. On average, the early metformin arm improved health outcomes and increased healthcare costs compared with usual care; however, significant uncertainty surrounded these mean point estimates. The differences in health outcomes and costs were not statistically significant, and when the uncertainty in the incremental cost and effect estimates was considered jointly, there was a low probability that

TABLE 2 Baseline maternal characteristics in EMERGE trial.

Variable	Early metformin *N* = 268	Placebo *N* = 267
Age (years) (Mean ± SD)	34.3 ± 4.9	34.3 ± 4.7
Body mass index at enrolment (Mean ± SD)	30.4 ± 6.4	30.7 ± 5.7
BMI < 30, % (*n*)	51.4% (131/255)	48.2% (121/251)
BMI>/=30, %(*n*)	48.6% (124/255)	51.8% 130/251)
Gestation at randomization		
Mean ± SD	25.4 ± 4.3	25.5 ± 4.1
Median (IQR)	27 (2.3)	27 (2.4)
Duration from randomisation to delivery		
Mean ± SD	13.7 ± 4.7	13.6 ± 4.3
Median (IQR)	12.3 (3.1)	12.4 (3.1)
Ethnic group, % (*n*)		
European or white	81.7% (219/268)	78.2% 209/267
African/Black	2.6% (7/268)	2.2% (6/267)
Asian	6.3% (17/268)	10.9% (29/267)
Irish traveller	4.1% (11/268)	0.7% (2/267)
Other	5.2% (14/268)	7.9% (21/267)
Education, % (*n*)		
Primary Only	3.4% (9/268)	1.1% (3/266)
Secondary Only	16.8% (45/268)	16.2% (43/266)
Tertiary education	79.9% (214/268)	82.7% 220/266
In receipt of Medical Card, % (*n*)	23.5% (63/268)	23.7% (63/266)
Private health insurance, % (*n*)	47% (126/268)	43.6% (116/266)
Unemployed, % (*n*)	7.1% (19/268)	10.2% (27/266)
Smoking during pregnancy, % (*n*)	6.3% (17/268)	6.4% (17/267)
Prior hypertension, % (*n*)	4.5% (12/268)	1.5% (4/266)
Nulliparous, % (*n*)	23.5% (63/268)	24% (64/267)
Previous Obstetrical history available, % (*n*)	87.8% (181/205)	84.7% 172/203
Gestational diabetes mellitus	35.9% (65/181)	37.2% (64/172)
Preeclampsia	13.3% (24/181)	13.4% (23/172)
Infant with birth weight >4000 g	31.5% (57/181)	25.6% (44/172)
Caesarean delivery	38.7% (70/181)	43% (74/172)
Infant with congenital anomaly	7.2% (13/181)	7.6% (13/172)
Previous Stillbirth	1.1% (2/181)	1.2% (2/172)
Antepartum Haemorrhage	11% (20/181)	8.7% (15/172)
Post-partum Haemorrhage	15.5% (28/181)	11.6% (20/172)
Blood pressure at randomisation—mm Hg (Mean ± SD)		
Systolic	114.9 ± 9.5	114.4 ± 9.2
Diastolic	68.9 ± 8.0	68.7 ± 8.8
Results of 75-g oral glucose-tolerance mmol/L (Mean ± SD)		
Plasma glucose level after overnight fast	5.2 ± 0.5	5.2 ± 0.5
1-Hr PP plasma glucose level	9.4 ± 1.9	9.7 ± 1.9
2-Hr PP plasma glucose level	7.1 ± 1.6	7.1 ± 1.6
Glycated hemoglobin at randomisation—(HbA1c) mmol/mol (Mean ± SD)	33.0 ± 3.4	32.9 ± 3.5

Abbreviations: BMI, body mass index; Hr PP, hour post-prandial; IQR, interquartile range; SD, standard deviation.

TABLE 3 Descriptive statistics for healthcare resource use, healthcare cost and health outcome data.

Variable	Description	Resource use		Costs (2022 € prices)	
Costs		Early metformin ($n = 268$), % (n)/Mean (SD)	Placebo ($n = 267$), % (n)/Mean (SD)	Early Metformin ($n = 268$), Mean (SD)	Placebo ($n = 267$), Mean (SD)
GDM care	Oral Glucose-Tolerance Test	100%	100%	46.27 (0)	46.27 (0)
	Lifestyle Advice Consultations	100%	100%	244.16 (0)	244.16 (0)
	Metformin	100%	0%	34.95 (3.51)	0 (0)
	Insulin	101 (37.69)	134 (50.19)	282.18 (426.96)	474.70 (543.25)
	Insulin days	26.95 (41.66)	35.82 (41.96)		
	Fast Acting Insulin Units/Day	5.99 (6.35)	10.42 (10.46)		
	Long Acting Insulin Units/Day	15.13 (8.57)	17.77 (7.01)		
	Laboratory Tests	100%	100%	225 (0)	225 (0)
	Blood Glucose Monitoring	100%	100%	204.29 (68.71)	202.16 (63.11)
Antenatal care	Ultrasound Scans	6.41 (4.32)	6.91 (5.84)	1296.43 (873.17)	1396.67 (1179.71)
	Hospital Outpatient Clinic Visits	9.31 (5.69)	9.73 (6.41)	1815.02 (1109.22)	1896.27 (1249.72)
	Hospital Inpatient Nights	0.88 (2.25)	0.68 (1.91)	870.03 (2221.76)	669.77 (1885.04)
	Hospital Day Cases	0.22 (0.92)	0.17 (0.72)	165.99 (707.91)	126.40 (549.94)
	Accident and Emergency Visits	0.82 (1.44)	0.85 (1.70)	272.75 (479.21)	281.24 (566.29)
	General Practice Visits	5.79 (4.81)	5.88 (5.65)	332.81 (276.55)	338.36 (324.91)
Delivery care	Normal Vaginal Delivery	122 (46.56)	122 (46.39)	3683.51 (1323.05)	3627.54 (1271.21)
	Instrumental/Assisted Vaginal Delivery	30 (11.45)	44 (16.73)		
	Elective Caesarean Section Delivery	57 (21.76)	50 (19.01)		
	Emergency Caesarean Section Delivery	53 (20.23)	47 (17.87)		
	Inpatient Length of Stay	2.38 (1.53)	2.26 (1.28)		
	Neonatal Intensive Care Unit			1380.93 (6134.58)	997.70 (5312.05)
	Admission	38 (14.50)	32 (12.17)		
	Length of Stay	1.20 (5.31)	0.86 (4.60)		

(Continues)

TABLE 3 (Continued)

Variable	Description	Resource use		Costs (2022 € prices)	
Costs		Early metformin ($n = 268$), % (n)/Mean (SD)	Placebo ($n = 267$), % (n)/Mean (SD)	Early Metformin ($n = 268$), Mean (SD)	Placebo ($n = 267$), Mean (SD)
Postnatal care	Hospital Outpatient Clinic Visits			129.92 (265.09)	122.11 (261.58)
	Mother	0.40 (1.13)	0.32 (1.08)		
	Infant	0.28 (0.64)	0.32 (0.80)		
	Hospital Inpatient Nights			662.84 (3072.49)	352.56 (1188.53)
	Mother	0.14 (0.60)	0.17 (0.85)		
	Infant	0.55 (3.10)	0.20 (0.83)		
	Hospital Day Cases			35.60 (214.69)	31.83 (168.52)
	Mother	0.04 (0.27)	0.02 (0.16)		
	Infant	0.00 (0.07)	0.03 (0.16)		
	Accident and Emergency Visits			126.17 (266.49)	126.84 (249.08)
	Mother	0.15 (0.45)	0.12 (0.39)		
	Infant	0.24 (0.58)	0.27 (0.61)		
	General Practice Visits			260.11 (99.96)	263.19 (112.76)
	Mother	1.87 (1.19)	1.83 (1.22)		
	Infant	2.75 (1.04)	2.84 (1.23)		
	Neonatal Intensive Care Units Admissions	0.00 (0.07)	0.02 (0.24)	32.72 (535.60)	164.20 (1931.39)
Total costs (€)	GDM Care Cost			1045.89 (470.50)	1197.61 (579.48)
	Antenatal Care Cost			4753.03 (3671.77)	4708.70 (3521.39)
	Delivery Care Cost			5064.45 (6353.21)	4625.24 (5672.19)
	Postnatal Care Cost			1251.64 (3274.10)	1078.44 (2432.69)
	Total Healthcare Cost			11947.54 (8232.03)	11321.50 (5567.93)

	Early Metformin ($n = 268$), Mean (SD)			Placebo ($n = 267$), Mean (SD)		
Health outcomes	Baseline	4 weeks, post-partum	12 weeks, post-partum	Baseline	4 weeks, post-partum	12 weeks, post-partum
EQ VAS Score	78.77 (13.96)	79.97 (14.33)	81.92 (12.03)	77.20 (16.10)	81.30 (12.30)	80.37 (14.84)
EQ-5D-5L Index Score	0.906 (0.007)	0.948 (0.006)	0.956 (0.007)	0.896 (0.008)	0.957 (0.005)	0.954 (0.093)
QALYs gained			0.468 (0.041)			0.465 (0.044)

TABLE 4 Incremental cost-effectiveness results: base-case analysis and selected sensitivity and subgroup analyses.

Description/analysis	Δ cost, mean difference estimate (SE) (*p*-value) (95% CI)	Δ QALY, mean difference estimate (SE) (*p*-value) (95% CI)	Probability that early metformin is cost-effective: threshold (λ) = €20,000 per QALY gained	Probability that early metformin is cost-effective: threshold (λ) = €45,000 per QALY gained	Probability that early metformin is cost-effective: threshold (λ) = €100,000 per QALY gained
Base-case analysis	193.07 (501.51) (0.700) (−789.88, 1176.01)	0.002 (0.006) (0.771) (−0.009, 0.013)	0.423	0.452	0.524
Sensitivity analysis					
Statistical analysis: univariate: covariates = Treatment Arm only	626.15 (639.18) (0.327) (−€626.62, €1878.92)	0.003 (0.004) (0.399) (−0.005, 0.011)	0.245	0.295	0.414
Cost analysis: GDM care	−148.89 (43.71) (0.001) (−234.57, −63.22)	0.002 (0.006) (0.771) (−0.009, 0.013)	0.951	0.817	0.715
Cost analysis: GDM care + antenatal care	−76.99 (326.00) (0.813) (−715.94, 561.97)	0.002 (0.006) (0.771) (−0.009, 0.013)	0.504	0.550	0.593
Cost analysis: GDM care + antenatal care + delivery care	29.10 (351.70) (0.934) (−660.21, 718.41)	0.002 (0.006) (0.771) (−0.009, 0.013)	0.435	0.483	0.545
Cost analysis: GDM care + antenatal care + delivery care + neonatal care costs	176.25 (411.41) (0.668) (−630.10, 982.60)	0.002 (0.006) (0.771) (−0.009, 0.013)	0.344	0.386	0.468
Statistical analysis: adjust for hospital setting	193.07 (280.71) (0.492) (−357.11, 743.24)	0.002 (0.006) (0.779) (−0.010, 0.014)	0.423	0.452	0.524
Statistical analysis: covariates: full set excluding socioeconomic variables	198.15 (525.30) (0.706) (−831.41, 1227.71)	0.002 (0.006) (0.773) (−0.009, 0.013)	0.427	0.469	0.523
Statistical analysis covariates: full set excluding gestational age	475.91 (600.64) (0.428) (−701.33, 1653.15)	0.000 (0.006) (0.992) (−0.012, 0.012)	0.214	0.246	0.338
Statistical analysis: covariates: full set excluding baseline utility	193.07 (501.51) (0.700) (−789.88, 1176.01)	0.007 (0.006) (0.258) (−0.005, 0.019)	0.357	0.489	0.649
Statistical analysis: alternative cost regression: gaussian/identity	657.12 (605.77) (0.278) (−530.17, 1844.41)	0.002 (0.006) (0.771) (−0.009, 0.013)	0.201	0.237	0.331

TABLE 4 (Continued)

Description/analysis	Δ cost, mean difference estimate (SE) (*p*-value) (95% CI)	Δ QALY, mean difference estimate (SE) (*p*-value) (95% CI)	Probability that early metformin is cost-effective: threshold (λ) = €20,000 per QALY gained	Probability that early metformin is cost-effective: threshold (λ) = €45,000 per QALY gained	Probability that early metformin is cost-effective: threshold (λ) = €100,000 per QALY gained
Statistical analysis: alternative cost regression: Gamma/Log	358.32 (514.42) (0.486) (−649.92, 1366.56)	0.002 (0.006) (0.771) (−0.009, 0.013)	0.325	0.368	0.436
Selected subgroup analysis					
Previous history of GDM cohort (Intervention $n = 64$; Placebo $n = 65$) Statistical analysis: cost: covariates: treatment arm: QALYs: covariates: treatment arm + baseline utility	−251.49 (1078.02) (0.816) (−2364.37, 1861.38)	0.016 (0.021) (0.446) (−0.025, 0.057)	0.661	0.716	0.752
Previous caesarean section cohort (Intervention $n = 71$; Placebo $n = 74$) Statistical analysis: cost: covariates: treatment arm: QALYs: covariates: treatment arm + baseline utility	−1174.94 (919.15) (0.201) (−2976.45, 626.56)	0.002 (0.018) (0.914) (−0.033, 0.036)	0.863	0.799	0.694

Note: QALYs Analysis: GLM regression model, with identity link function, Gaussian variance function, estimated controlling for treatment group and other covariates. Full covariate set: age, ethnicity, first pregnancy status, previous caesarean section status, previous GDM, status, medical condition status, smoking status, body mass index at screening, employment status, educational attainment status, marital status medical card status, private health insurance status, private consultant status, gestational age at screening, baseline utility. Cost Analysis: GLM regression model, with log link function, Inverse Gaussian variance function, estimated controlling for treatment group and other covariates. Full covariate set; age, ethnicity, first pregnancy status, previous caesarean section status, previous GDM, status, medical condition status, smoking status, body mass index at screening, employment status, educational attainment status, marital status medical card status, private health insurance status, private consultant status, gestational age at screening. Expected Cost-effectiveness Analysis: Present probabilities that early metformin is cost-effective for a range of cost-effectiveness threshold values (λ) per QALY gained. Probabilistic estimates generated using non-parametric bootstrapping technique employing 1000 replications.

the early metformin arm would be considered cost-effective at potential decision-making threshold values for Ireland (€20,000: 0.423; €45,000: 0.452). The base-case and sensitivity analyses failed to offer definitive evidence in favour of early GDM treatment with metformin, given that the observed cost, QALY and cost-effectiveness outcomes were consistent with chance and the related decision uncertainty was significant. These findings supplement those from the parallel clinical effectiveness analysis, which reported that early metformin in addition to usual care was not superior to usual care in terms of the composite primary outcome in the trial.[20] Notably, that study did report a series of positive impacts of early metformin on secondary maternal and neonatal outcomes,[20] which when considered alongside our findings for non-significant differences in economic outcomes, point to further research questions worthy of examination.

The possible sources of the observed uncertainty in the economic evaluation are worth considering. In terms of the health outcome analysis, the QALYs gained variable was determined by EQ-5D-5L responses at baseline and two follow-up points, at 4 weeks and 12 weeks postpartum. This raises the concern that potential differential quality of life impacts between the early metformin and placebo arms may have been missed along the antenatal and delivery care pathway. Indeed, the choice of the QALY measure in the context of pregnancy and the likelihood of observing a clinically important difference between intervention and control over the trial follow-up period are open to question. For example, a recent economic evaluation in the GDM field by Haque et al.[28] presented expected cost-effectiveness probabilities for a range of threshold values per composite adverse GDM pregnancy outcome prevented. Following this approach, we estimate that if decision-makers were willing to pay €500 or more to prevent an additional adverse composite outcome, there would be an over 90% probability of early metformin being cost-effective. However, no explicit evidence exists for what decision-makers in Ireland or elsewhere would be willing to pay to improve GDM outcomes.

In respect of costing, while the early metformin arm was associated with higher healthcare costs relative to usual care, this was predominately driven by the combination of non-statistically significant increases in the costs of Delivery Care and Postnatal Care, which outweighed the observed reductions in GDM Care costs. Further, the exploratory subgroup analyses produced several preliminary findings of note. We report higher expected cost-effectiveness results for the previous GDM cohort (€20,000: 0.661; €45,000: 0.716) and the previous caesarean section cohort (€20,000: 0.863; €45,000: 0.799). For these analyses, the observed reductions in the mean costs of care in the early metformin arm were the key driver in the improved cost-effectiveness results. That said, care should be taken in interpreting these supplementary findings as the trial was not powered to detect differences within these subgroups, nor did we pre-specify these analyses in the protocol or analysis plans. Further, consideration should be given to the clinical and ethical rationale for segregating the overall GDM population into such subgroups, and the á priori expectations for the potential impacts of early metformin in each case. This notwithstanding, these estimates suggest evidence of promise and point to avenues for further research.

This study had several strengths and limitations. The economic evaluation was based on a RCT, which included a representative cohort of GDM women across all BMI categories, thereby increasing the greater generalisability of the results. Despite the COVID-19 pandemic, there was low attrition and high adherence to treatment allocation, and data on 98% of pregnancies were available for statistical analysis. Given the data collection processes, missing data was not a significant consideration and were not systematically different between arms. Given the healthcare perspective adopted, the study included a comprehensive range of healthcare resources for inclusion in the cost analysis. Further, results remained robust in a series of alternative approaches considered in sensitivity analysis.

There were several limitations relating to the conduct of the RCT, as outlined in the main trial publications,[19,20] which also applied to the economic evaluation. The trial population consisted of 80% white European women, which reflects the Irish population but limits the generalisability of results to jurisdictions with a wider distribution of ethnicity. In terms of the economic evaluation methods, the time horizon was limited to the trial follow-up period of 26 weeks, thereby excluding costs and benefits that are likely to arise over the remainder of the patients' lifetime. This may be relevant given the link between GDM and future diagnosis of type 2 diabetes,[7–9] and if there exists a possibility for divergences in the long-term cost-effectiveness between early metformin and usual care. For example, significant improvements in maternal outcomes at 12 weeks follow-up, including self-reported capillary glycaemic control and gestational weight gain,[20] have the potential to translate into longer term differences in health outcomes and costs beyond the end of the trial. These questions warrant further research and will be considered in the EMERGE follow-up study.

The variation in the trial follow-up period is also worth noting, although there is no significant difference across treatment arms. That is, given the nature of the pregnancy care pathway, the treatment period with metformin and placebo varied within each treatment arm but was similar

across arms: 14.13 (SD: 4.66) weeks in the intervention arm versus 14.02 (SD: 4.28) weeks in the control arm. Relatedly, follow-up was variable within the treatment arm but similar across arms: 26.13 (SD: 4.66) weeks in the intervention arm versus 26.02 (SD: 4.28) weeks in the control arm. Notably, we also included gestational age as a covariate in the multivariable regression analysis.

It should be noted that the sample size calculation for the trial was based on the primary composite outcome clinical endpoint and may be insufficient to detect statistically significant changes in the cost and QALY outcomes considered in the economic evaluation. As stated above, similar concerns relate to the subgroup analysis results presented. While the cost analysis was conducted from the healthcare perspective, other resource items were not captured. That said, there is little evidence to suggest that including additional costs would fundamentally alter the findings presented. Finally, the process of conducting cost analysis in Ireland is compromised by the lack of nationally available unit cost data. In estimating unit costs, we endeavoured to be conservative in any assumptions adopted.

AUTHOR CONTRIBUTIONS

FD, AE, AS, DD, CN and MOD devised the concept for this trial, wrote the protocol and led the conduct of the trial. AAI and JF performed statistical analyses on the trial. POS oversaw biochemical analysis of laboratory samples. PG and RM designed and conducted the health economics analysis. POS oversaw biochemical analysis of laboratory samples. PG, RM and FD drafted and revised the manuscript. All authors approved the final version of the manuscript and are accountable for the integrity of the work.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare with respect to the study. Dr. Dunne reported nonfinancial support from Merck and matched placebo and nonfinancial support from Ascensia blood glucose-monitoring equipment during the conduct of the study. The trial was funded by the HRB of Ireland; coordinated by the HRB-Clinical Research Facility Galway; and received nonfinancial support from Merck Healthcare KGaA. Metformin and matched placebo were provided by Merck Healthcare KGaA, Darmstadt, Germany and blood glucose-monitoring strips by Ascensia during the conduct of the study.

DATA AVAILABILITY STATEMENT

Data from this trial will not be shared.

ROLE OF THE FUNDER

HRB of Ireland and the University of Galway had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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