Supplemental Folate Intake Modifies the Relation Between Traffic-Related Air Pollution and Live Birth Among Women Undergoing Assisted Reproduction

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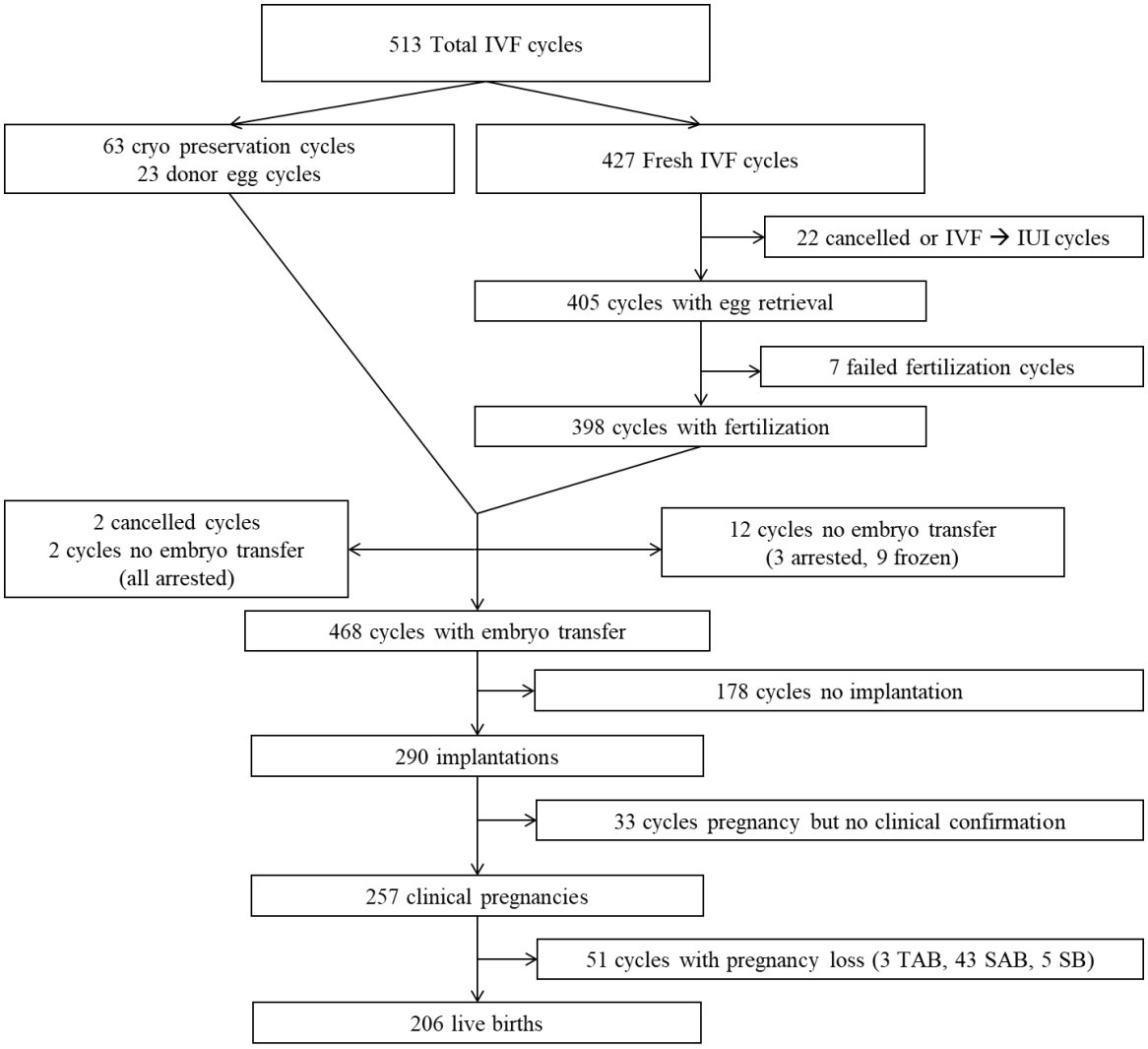
Web Figure 1. Overview of the Outcomes of the 513 Initiated Assisted Reproductive Technology (ART) Cycles in the Environmental and Reproductive Health (EARTH) Study, 2005-2015.



Abbreviations: SAB, spontaneous abortion; SB, stillbirth; TAB, therapeutic abortion; IUI, intrauterine insemination; IVF, in vitro fertilization.

Web Table 1. Spearman Correlations Between Distance to A1-A3 Roadways and Estimated Nitrogen Dioxide (NO2), Ozone (O3), Particulate Matter <2.5 µm (PM2.5), and Black Carbon (BC) Levels in the 3 months prior to ART among 304 women in the EARTH Study, 2005-2015.

	Distance to A1-A3 Roadways	**NO_2**	**O_3**	**$PM_{2.5}$**	**BC**
Distance to A1-A3 Roadways	1.0	-0.39	0.09	-0.09	-0.48
NO_2		1.0	-0.13	0.06	0.39
O_3			1.0	0.11	-0.22
$PM_{2.5}$				1.0	0.24
BC					1.0

Abbreviations: ART, assisted reproductive technology; BC, black carbon; EARTH, Environment and Reproductive Health; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter <2.5 µm.

Web Table 2. Joint Associations Between Total and Supplemental Folate Intake, Estimated Air Pollution Exposures in the 3 Months Prior to ART and Risk of Live Birth in the EARTH Study, 2005-2015.

	Pollutant < or ≥ median	Total Folate < or ≥ 1000 µg/day	Number of Live Births/Cycles	Adjusted RR (95% CI) of Live Birth[a]	RERI (95% CI)[b]
Distance to A1-A3 Roadways	High	High	52/119	1.0 (REF)	
		Low	51/139	0.79 (0.58, 1.06)	
	Low	High	67/155	0.98 (0.74, 1.30)	
		Low	36/100	0.76 (0.56, 1.02)	-0.01 (-0.38, 0.37)
NO_2	Low	High	59/135	1.0 (REF)	
		Low	50/123	0.86 (0.64, 1.14)	
	High	High	60/139	0.96 (0.72, 1.28)	
		Low	37/116	0.67 (0.50, 0.90)	-0.15 (-0.52, 0.23)
$PM_{2.5}$	Low	High	59/135	1.0 (REF)	
		Low	41/118	0.74 (0.56, 0.99)	
	High	High	60/139	0.86 (0.67, 1.11)	
		Low	46/121	0.71 (0.54, 0.93)	0.10 (-0.23, 0.43)
O_3	Low	High	59/140	1.0 (REF)	
		Low	46/116	0.82 (0.62, 1.10)	
	High	High	60/134	0.99 (0.76, 1.30)	
		Low	41/123	0.73 (0.55, 0.98)	-0.08 (-0.47, 0.31)
BC	Low	High	55/129	1.0 (REF)	
		Low	49/133	0.84 (0.64, 1.11)	
	High	High	64/145	1.01 (0.77, 1.31)	
		Low	38/106	0.73 (0.52, 1.02)	-0.12 (-0.50, 0.26)
	Pollutant < or ≥ median	**Supplemental Folate < or ≥ 800 µg/day**	**Number of Live Births/Cycles**	**Adjusted RR (95% CI) of Live Birth[a]**	**RERI (95% CI)[b]**
Distance to A1-A3 Roadways	High	High	41/89	1.0 (REF)	
		Low	62/169	0.76 (0.56, 1.03)	
	Low	High	51/121	0.92 (0.68, 1.25)	
		Low	52/134	0.79 (0.59, 1.06)	0.11 (-0.26, 0.47)
NO_2	Low	High	45/107	1.0 (REF)	
		Low	64/151	0.98 (0.72, 1.33)	
	High	High	47/103	1.12 (0.82, 1.54)	
		Low	50/152	0.74 (0.54, 1.01)	-0.36 (-0.82, 0.09)
$PM_{2.5}$	Low	High	46/101	1.0 (REF)	
		Low	54/152	0.76 (0.57, 1.00)	
	High	High	46/109	0.84 (0.63, 1.12)	
		Low	60/151	0.72 (0.55, 0.94)	0.12 (-0.20, 0.45)
O_3	Low	High	46/101	1.0 (REF)	
		Low	59/155	0.75 (0.57, 0.99)	
	High	High	46/109	0.86 (0.64, 1.15)	
		Low	55/148	0.75 (0.57, 0.97)	0.13 (-0.21, 0.47)
BC	Low	High	42/101	1.0 (REF)	
		Low	62/161	0.92 (0.69, 1.22)	
	High	High	50/109	1.09 (0.81, 1.46)	
		Low	52/142	0.79 (0.57, 1.09)	-0.21 (-0.65, 0.22)

Abbreviations: ART, assisted reproductive technology; BC, black carbon; EARTH, Environment and Reproductive Health; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter <2.5 µm; RERI, relative excess risk due to interaction.

[a]Analyses were run using generalized estimating equations with binomial distribution and log link function adjusted for age, BMI, race, and smoking status, education level, initial infertility diagnosis, and year of cycle start

[b]RERI was calculated as RR_{11}-R_{10}-R_{01}+1 and the 95% confidence interval was estimated using approximate variance estimators (Hosmer & Lemeshow, 1992)

Web Table 3. Effect Modification of Supplemental Folate intake on the Relationship between Estimated Nitrogen Dioxide (NO_2) Concentrations in the 3 Months Prior to ART and Intermediate Outcomes in the EARTH Study, 2005-2015.

	Adjusted Beta Coefficient or Percent Change (95% CI)[a] per 20 ppb increase in NO_2		
	<800 μg/day of supplemental folate	≥800 μg/day of supplemental folate	*P* for interaction[b]
Estradiol Trigger[c], pmol/L	1.4 (-98.1, 100.9)	-2.3 (-56.7, 52.1)	0.15
Endometrial Thickness, mm	-0.21 (-0.43, 0.02)	0.08 (-0.10, 0.25)	0.12
Total Oocyte Yield, N	-0.9 (-5.6, 4.1)	1.4 (-2.1, 5.0)	0.42
Mature Oocyte Yield, N	-2.3 (-7.2, 2.8)	1.9 (-1.6, 5.5)	0.16

Abbreviations: ART, assisted reproductive technology; CI, confidence interval; EARTH, Environment and Reproductive Health; IQR, interquartile range; NO_2, nitrogen dioxide.

[a]All analyses were conducted using generalized linear mixed models with random intercepts, normal (for estradiol levels and endometrial thickness) or Poisson (for oocyte counts) distribution and identity (for estradiol levels and endometrial thickness) or log (for oocyte counts). Data are adjusted for age, BMI, race, smoking status, education level, infertility diagnosis, and year of cycle start.

[b]*P* for interaction was calculated by including an interaction term in the multivariable model.

[c]The analysis of intermediate outcomes included 278 women (405 fresh ART cycles).

Web Table 4. Sensitivity Analyses for the Effect Modification of Supplemental Folate Intake on the Relationship Between Estimated Nitrogen Dioxide (NO_2) Concentrations in the 3 Months Prior to ART and Odds of Live birth in Women from the EARTH Study, 2005-2015.

	Adjusted OR of Live Birth (95% CI)[a]				
	n	<800 µg/day of supplemental folate	n	≥800 µg/day of supplemental folate	*P* for interaction[b]
Nitrogen Dioxide (NO_2), per 20 ppb					
Non-Current Smokers (n=501)	294	0.76 (0.58, 0.99)	207	1.05 (0.86, 1.29)	0.02
No Donor Egg or Cryo Cycles (n=427)	250	0.79 (0.60, 1.05)	177	1.02 (0.82, 1.25)	0.02
Cycles with Embryo Transfer (n=468)	269	0.76 (0.58, 1.00)	199	1.05 (0.86, 1.29)	0.04
Cycles with Prospective Diet (n=495)	298	0.75 (0.57, 0.97)	197	1.03 (0.84, 1.27)	0.01
First In Study ART Cycle (n=304)[c]	173	0.70 (0.49, 1.01)	131	0.93 (0.72, 1.19)	0.04
First ART Cycles Only (n=235)[c]	135	0.73 (0.50, 1.07)	100	0.89 (0.66, 1.20)	0.06
Nulligravid Women Only (n=300)	185	0.74 (0.54, 1.03)	115	1.03 (0.82, 1.29)	0.13

Abbreviations: ART, assisted reproductive technology; CI, confidence interval; EARTH, Environment and Reproductive Health; NO_2, nitrogen dioxide.

[a]Analyses were run using multivariable generalized linear mixed models with random intercepts (binomial distribution and logit link function) adjusted for age, BMI, race, and smoking status, education level, initial infertility diagnosis, and year of ART cycle.

[b]*P* for interaction was calculated by including an interaction term in the multivariable model.

[c]Analyses were run using multivariable logistic regression models adjusted for age, BMI, race, and smoking status, education level, initial infertility diagnosis, and year of ART cycle.

Web Table 5. Co-Pollutant Models for the Effect Modification of Total and Supplemental Folate Intake on the Relation Between Estimated Nitrogen Dioxide (NO_2), Ozone (O_3), Fine Particulates ($PM_{2.5}$), and Black Carbon (BC) Concentrations in the 3 Months Prior to ART and Odds of Live Birth in the EARTH Study, 2005-2015.

	Adjusted OR of Live Birth (95% CI)[a]		
	<1000 µg/day of total folate	≥1000 µg/day of total folate	*P* for interaction[b]
NO_2, per 20 ppb	0.75 (0.53, 1.05)	0.98 (0.81, 1.20)	0.02
O_3, per 15 ppb	0.89 (0.78, 1.02)	1.02 (0.91, 1.14)	0.14
$PM_{2.5}$, per 3 µg/m^3	1.06 (0.53, 2.12)	0.77 (0.41, 1.45)	0.96
BC, per 0.2 µg/m^3	1.25 (0.77, 2.04)	1.11 (0.79, 1.56)	0.79
	Adjusted OR of Live Birth (95% CI)[a]		
	<800 µg/day of supplemental folate	≥800 µg/day of supplemental folate	*P* for interaction[b]
NO_2, per 20 ppb	0.71 (0.53, 0.97)	1.04 (0.84, 1.28)	0.01
O_3, per 15 ppb	0.91 (0.82, 1.02)	1.04 (0.91, 1.19)	0.13
$PM_{2.5}$, per 3 µg/m^3	1.03 (0.56, 1.89)	0.78 (0.37, 1.61)	0.99
BC, per 0.2 µg/m^3	1.24 (0.83, 1.87)	1.26 (0.84, 1.89)	0.42

Abbreviations: ART, assisted reproductive technology; BC, black carbon; EARTH, Environment and Reproductive Health; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter <2.5 µm.

[a]Analyses were run using multivariable generalized linear mixed models with random intercepts (binomial distribution and logit link function) adjusted for age, BMI, race, and smoking status, education level, initial infertility diagnosis, year of cycle start, and the other pollutants.