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Preconception serum lipids and lipophilic micronutrient levels are associated with live birth rates after in vitro fertilization

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Abstract

Research Question—Is a mixture of preconception serum lipids and lipophilic micronutrients associated with pregnancy and live birth outcomes?

Design—In this prospective cohort study, blood serum was collected on the day of oocyte retrieval for 180 women undergoing IVF at an academic reproductive health center. Concentrations of lipids (phospholipids, total cholesterol, high- and low-density lipoproteins, and triglycerides) and lipophilic micronutrients (α-, δ-, and γ-tocopherols, retinol, β- and α-carotenes, β-cryptoxanthin, lutein, and lycopene) were determined using diagnostic reagent kits and high-performance liquid chromatography. Using Poisson regression with robust variance estimation, we evaluated changes in Z-scores for the mixture of serum lipid and lipophilic micronutrient concentrations as predictors of embryo implantation, clinical pregnancy, and live birth, adjusted for age, body mass index (BMI), race, smoking status, infertility diagnosis, ovarian stimulation protocol, and other measured lipid and lipophilic micronutrient concentrations.

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Conflict of interest

The authors have declared no conflicts of interest with respect to this work.

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Results—Each standard deviation (SD) higher serum triglyceride concentration was associated with a lower chance of live birth (RR=0.54; 95% CI=0.33-0.90) whereas a 1 SD higher serum α-tocopherol concentration, as part of a mixture of serum lipids and lipophilic micronutrients, was associated with a higher likelihood for a live birth (RR=1.61; 95% CI=1.11-2.36). Serum β-carotene concentrations were associated with live birth in a non-linear fashion; low β-carotene was associated with a lower chance of live birth and high β-carotene with a higher chance of live birth.

Conclusion—While components of a mixture of lipids and lipophilic micronutrients were associated with live birth outcomes following IVF, a larger investigation is necessary to fully evaluate the potential clinical implications.

Keywords

In vitro fertilization (IVF); lipids; live birth; micronutrients; alpha-tocopherol

Introduction

Lipids and lipophilic micronutrients have become of increasing interest as potential risk factors for in vitro fertilization (IVF) outcomes, given myriad roles played in reproduction (Fujimoto et al. 2010a, Arhin et al. 2017). Their various anti-oxidant and inflammatory activities are likely to affect female reproduction (Cetin et al. 2010, Agarwal et al. 2012). Characterizing the impact of lipids and lipophilic micronutrients on IVF outcomes may offer an opportunity for non-invasive clinical interventions to improve live birth rates.

High density lipoprotein (HDL) particles transport cholesterol to pre-ovulatory ovarian follicles in support of steroidogenesis and have anti-inflammatory and antioxidant properties (Fujimoto et al. 2010a, Yen et al. 2014). Low density lipoprotein (LDL) and triglycerides are necessary for post ovulatory ovarian hormone synthesis and embryonic and fetal development (Herrera 2002, Woollett 2011). Lipophilic micronutrients, including vitamins A, D, E, K, and carotenes, are sourced naturally from dietary vegetables, fruits, and animal products, and select forms are found in dietary supplements (U.S. Centers for Disease Control and Prevention 2012). Yet, circulating concentrations of vitamins E (tocopherol) and A (retinol) are regulated by the liver, in which they are stored. Vitamin E and the carotenoids, including α-carotene, β-cryptoxanthin, lutein, zeaxanthin, and others, act as antioxidants (Sies and Stahl 1995) and are critical for zygote implantation, placental maturation, and embryogenesis (Kaempf-Rotzoll et al. 2003, Jishage et al. 2005, Miller et al. 2012). α-carotene and β-cryptoxanthin are also precursors for vitamin A (retinol) synthesis, which is critically important for early embryo implantation (Fazleabas et al. 1994) and development (Zile 2001).

Several studies have demonstrated associations between circulating lipid and lipophilic micronutrient concentrations and reproductive outcomes. In IVF populations, lipid concentrations have been associated with embryo quality and clinical pregnancy rates (Browne et al. 2008, Browne et al. 2009, Onyiaodike et al. 2018). Furthermore, higher plasma and/or follicular fluid (FF) concentrations of lipophilic micronutrients have been associated with a larger number of mature oocytes retrieved, better embryo quality, and higher pregnancy rates after IVF (Palini et al. 2014). In couples conceiving spontaneously

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higher serum cholesterol concentrations were associated with reduced fecundability (Schisterman et al. 2014), and higher serum cholesterol and lower serum HDL lipid concentrations were associated with lower rates of implantation (Pugh et al. 2017).

Despite evidence supporting associations between individual lipids and lipophilic micronutrients and reproductive outcomes, the results of epidemiologic studies have been inconsistent (Arhin et al. 2017, Haider and Bhutta 2017). To the best of our knowledge no studies to date have investigated a mixture of lipids and lipophilic micronutrients simultaneously in relation with pregnancy and live birth outcomes among women undergoing IVF. A mixture should more closely approximate biology than is achieved by evaluating isolated associations. To help to address the pending data gap, we investigated associations between a mixture of serum lipid and lipophilic micronutrient concentrations and pregnancy outcomes in an exploratory analysis of women undergoing IVF.

Materials and Methods

Sample selection and data collection

Sample selection and clinical protocols were described in detail in prior publications (Bloom et al. 2014, Kim et al. 2017b). In brief, we enrolled 180 of 184 (97.8%) sequential female patients using fresh, non-donor oocytes for IVF, at the University of California at San Francisco (UCSF) Center for Reproductive Health, between April 2010 and June 2011.

The women followed standard clinical protocols for controlled gonadotropin-induced ovarian stimulation (COS), followed by subcutaneous administration of human chorionic gonadotropic (hCG) when a sufficient number of follicles had developed to at least 17 millimeters in diameter. Thirty-six hours later, oocytes were retrieved using ultrasound-guided transvaginal fine needle aspiration. Oocytes were fertilized using fresh sperm via intracytoplasmic sperm injection (ICSI) or conventional IVF on the day of oocyte retrieval. Embryos were transferred between 2 and 5 days later, and implantation was determined according to initial and confirmatory serum hCG tests approximately 2 weeks later. Clinical pregnancy was confirmed by ultrasound visualization of ≥1 gestational sacs at 6-7 weeks gestation. Obstetricians were contacted at approximately 9 months gestation to identify delivery of at least one live born infant.

Women completed a study questionnaire to capture demographic and lifestyle factors, and provided a fasting blood specimen, collected on the day of oocyte retrieval. We abstracted primary infertility diagnosis, COS protocol, and IVF outcomes from the electronic medical record. We excluded n=13 without embryo transfers from the current study, leaving n=167 analyzed.

Serum lipid and lipophilic micronutrient concentrations

Blood lipid and lipophilic micronutrient concentrations were measured by the Clinical Biochemistry and Oxidative Stress Laboratory at the University of Buffalo, State University of New York. We used FDA approved diagnostic reagent kits, calibrators, and quality control materials from Sekisui Diagnostics (Lexington, MA USA). Calibrators consisted of DC-Cal multi-analyte calibrator. Quality control (QC) for phospholipids, total cholesterol,

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HDL-cholesterol, and triglycerides were monitored according to Sekisui's DC-TROL three-level QC material. Total cholesterol, HDL-cholesterol, and triglycerides were adapted to a Cobas Fara II automated chemistry analyzer (Hoffmann-La Roche, Basel, Switzerland). Phospholipids were adapted to the ABX Pentra 400 automated chemistry analyzer (Horiba Scientific Instruments, Ervine, CA USA). Autoanalyzers were programmed using application parameters provided by the kit manufacturer. Average interassay coefficients of variation (CVs) ranged from 4.4% for total cholesterol to 10.3% for phospholipids. We used the Friedewald equation to estimate LDL from total cholesterol, HDL, and triglyceride concentrations (Friedewald et al. 1972, Warnick et al. 1990). We used high-performance liquid chromatography (HPLC) to determine concentrations of lipophilic micronutrients (α-, δ-, and γ-tocopherols, retinol, β- and α-carotenes, β-cryptoxanthin, lutein, and lycopene) in serum, according to a previously described method (Browne and Armstrong 1998). Average interassay CVs ranged from 6.5% for retinol to 13.9% for α-carotene, across several levels of QC material. The Clinical Biochemistry and Oxidative Stress Laboratory successfully participates in the National Institute of Standards and Technology (NIST) micronutrients measurement quality assurance program and used reference material NIST SRM 968C, Fat-Soluble Vitamins and Carotenoids in Human Serum.

Statistical analysis

We described distributions of baseline demographic and clinical factors and serum concentrations of lipids and lipophilic micronutrients among women who had an embryo transfer. We evaluated bivariate associations between serum lipid and lipophilic micronutrient concentrations using Spearman rank correlation coefficients, as well as associations with demographic and clinical factors. This allowed us to identify potential multicollinearity problems for our subsequent multivariable regression models. We identified potential confounding variables for adjustment in multivariable models *a priori* from the scientific literature, as common causes preceding both IVF outcomes and serum lipid or lipophilic micronutrient concentrations, and incorporated these into a directed acyclic graph (Greenland et al. 1999) (DAG; Supplemental Figure 1). These included: self-reported race, categorized as Asian vs. non-Asian (Fujimoto et al. 2010b), age in years (Maheshwari et al. 2008, Zhang et al. 2016), BMI in kg/m^2 (Supramaniam et al. 2018), self-reported history of cigarette smoking as "ever" vs. "never" (Hughes and Brennan 1996, Klonoff-Cohen et al. 2001, Alberg 2002, Fuentes et al. 2010), primary infertility diagnosis as female factor-diminished ovarian reserve (DOR) vs. female factor-non DOR (including endometriosis, tubal factor, polycystic ovary syndrome, anovulation, and recurrent pregnancy loss) vs. male factor or preimplantation genetic diagnosis (PGD) vs. unexplained, and COS protocol, including antagonist protocols vs. flare protocols (including clomid flare and microdose flare) vs. Lupron down regulated (LDR; including long luteal, demi-halt, and very low dose leuprolide acetate protocols) (Bloom et al. 2014, Shrestha et al. 2015, Pacchiarotti et al. 2016). We did not adjust for clinical activities that took place after blood specimen collection in our main models, including the number of embryos transferred and fertilization method (ICSI vs. conventional IVF), These were intervening variables in the causal pathway between lipids/lipophilic micronutrients and clinical IVF outcomes according to our DAG (Supplemental Figure 1), and so adjustment would bias the results (Schisterman et al. 2009).

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Based on substantial heterogeneity in the ranges of the serum lipid and lipophilic micronutrient concentrations, we scaled all values to standard deviations (SDs) as Z-scores prior to multivariable analysis. Some participants were missing values for some variables (8% for lipids, 5% for race, 4% for lipophilic micronutrients, and 4% for smoking). We implemented a Markov chain Monte Carlo multiple imputation procedure, with 50 imputed data sets, to accommodate these missing values, under an assumption of missing at random (Hamra et al. 2013). We first specified modified Poisson regression models simultaneously including all serum lipid and lipophilic micronutrient concentrations as predictors of implantation, clinical pregnancy, or live birth, to characterize the effects conditional on other serum lipid and lipophilic micronutrient concentrations. We next allowed for non-linear associations by incorporating quadratic terms for serum lipid and lipophilic micronutrient concentrations into the models, retaining those with $p<0.10$. Lastly, we adjusted for age, BMI, race, smoking status, primary infertility diagnosis, and COS protocol as confounding variables.

We conducted sensitivity analyses to evaluate the robustness of our results. First, we further adjusted the final models for the number of embryos transferred and for the fertilization method to assess the impact. Second, we limited the analysis to non-Asian participants only to evaluate the possibility for modification of the associations by race. Third, we limited the analysis to n=144 participants with complete case information. Finally, we conducted an "intent-to-treat" type analysis, including all n=180 irrespective of embryo transfer (Messerlian and Gaskins 2017).

For all regression models, we excluded influential observations with Dfbeta > |1.96| for lipid or lipophilic micronutrient concentrations and repeated the analysis. We defined statistical significance for a two-tailed test as $p<0.05$ *a priori*. Confounder-adjusted models were individually corrected for multiple comparisons using the false discovery rate, which quantifies the likelihood for a false-positive result among the positive findings and which we expressed as the p-value analogous q-value (Storey 2002). We used SAS v.9.2 (SAS Institute, Inc. Cary, NC USA) for statistical analysis. We used PASS v.12 (NCSS, LLC Kaysville, UT USA) to estimate *post hoc* statistical power to detect associations between lipids/lipophilic micronutrient and live birth, adjusted for confounding variables, with $\alpha=0.05$.

All participants completed written informed consent and the UCSF Committee on Human Research approved the study protocol.

Results

Distributions of demographic and clinical factors for 167 women that had an embryo transfer are presented in Table I. On average, women were 37.2 years old, ranging from 25 to 45 years old, with BMI of 24.3 kg/m^2. There were n=109 white, n=46 Asian, and n=3 African American participants with embryo transfers, and most had never smoked cigarettes (88.8%). Clinically, the LDR ovarian stimulation protocol was used most widely (67.1 %), 11.9 oocytes were retrieved and 6.2 embryos obtained on average. Most women had day 3 transfers (n=46 day 2, n=90 day 3, and n=31 day 5). Most women (54.5%; n=91) achieved

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embryo implantation, 37.1% (n=62) had a clinical pregnancy, and 28.7% (n=48) had a live birth during the study cycle. There were no significant associations between the infertility diagnosis and the implantation, clinical pregnancy, and live birth outcomes (data not shown).

Distributions of serum lipid and lipophilic micronutrient concentrations are presented in Table II. The mean (SD) concentration of phospholipids was 210.8 mg/dL (33.4), HDL was 55.8 mg/dL (13.1), LDL was 83.8 mg/dL (23.3), and triglycerides was 113.6 mg/dL (65.6). Concentrations of α-tocopherol, β-carotene, β-cryptoxanthin, and lutein were higher in this cohort than the geometric mean levels for U.S. women 20 to 39 years of age, ranging from 22% higher for α-tocopherol to 128% higher for β-carotene (U.S. Centers for Disease Control and Prevention 2012). Concentrations of retinol were similar to the general population, while concentrations of γ-tocopherol were 74% lower and those for α-carotene were 19% lower than the general population (U.S. Centers for Disease Control and Prevention 2012). Lipid measures for women in our study fell within age-specific clinical reference intervals (Burtis et al. 2013, Mayo 2018) with few exceptions (9% for phospholipids, 10% for HDL, 33% for LDL, and 11% for triglycerides).

The unadjusted, bivariate associations between serum lipid and lipophilic micronutrient concentrations with demographic and clinical factors can be found in Supplemental Table I. Concentrations of HDL, β-carotene, α-carotene, β-cryptoxanthin, and lutein were higher in women with a BMI < 25 kg/m^2, whereas concentrations of LDL, triglycerides, and γ-tocopherol were higher in women with a BMI ≥ 25 kg/m^2. Furthermore, Asian women had higher median concentrations of triglycerides and β-cryptoxanthin compared to non-Asian women (108.0 vs. 92.4 mg/dL, p=0.04 and 0.14 vs. 0.09 μg/mL, p=0.004, respectively), γ-tocopherol concentrations varied by primary infertility diagnosis (p=0.02), with the median level among women with a non-DOR female infertility diagnosis (0.25 μg/mL) significantly lower than concentrations for women with DOR, male/PGD, or unexplained primary infertility diagnoses. Phospholipid and triglyceride concentrations were significantly associated with the number of oocytes retrieved (r=0.18, p=0.02 and r=0.23, p=0.004, respectively) and total embryos (r=0.17, p=0.03 and r=0.26, p=0.001, respectively), and concentrations of LDL were significantly associated with the number of oocytes retrieved (r=−0.16, p=0.05).

The unadjusted bivariate associations among serum lipid and lipophilic micronutrient concentrations are shown in Supplemental Table II. There were multiple statistically significant, yet weak, correlations; the strongest correlation was for phospholipids with α-tocopherol concentrations (r=0.61, p<0.0001).

Supplemental Table III contains the unadjusted results of modified Poisson regression models for clinical IVF outcomes, simultaneously including a mixture of lipids and lipophilic micronutrients as predictors in the same model. Table III expands upon the results in Supplemental Table III by adjusting for maternal age, BMI, race, smoking status, primary infertility diagnosis, and COS protocol. Women with 1 SD higher serum β-cryptoxanthin concentration were 18% less likely to achieve embryo implantation compared to women with average concentrations (relative risk [RR]=0.82; 95% confidence interval [CI]=0.68-0.99; p=0.04; q=0.55), adjusted for demographic and clinical confounders. We

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identified a significant confounder-adjusted non-linear association for clinical pregnancy and β-carotene (p=0.01; q=0.16). A 1 SD higher β-carotene concentration, compared to mean concentrations, was associated with an overall 15% lower (RR=0.85; 95% CI=0.64-1.12) likelihood of clinical pregnancy, a 2 SD higher concentration was associated with a 7% lower (RR=0.93; 95% CI=0.59-1.46) likelihood of clinical pregnancy, and a 3 SD higher concentration was associated with a 31 % higher (RR=1.31; 95% CI=0.68-2.51) likelihood for a clinical pregnancy. A 1 SD higher lycopene concentration was associated with a borderline significant 20% lower likelihood for clinical pregnancy (RR=0.80; 95% CI=0.64, 1.003; p=0.05; q=0.31), adjusted for confounders. In the confounder-adjusted live birth models, women with 1 SD higher triglyceride levels were 46% less likely to have a live birth relative to women with average triglyceride levels (RR=0.54; 95% CI=0.33, 0.90; p=0.02; q=0.05). Furthermore, women with 1 SD higher α-tocopherol concentrations were 61 % more likely to have a live birth compared to women with average α-tocopherol concentrations (RR=1.61; 95% CI=1.11-2.36; p=0.01; q=0.05). Lastly, consistent with the clinical pregnancy model, we identified a statistically significant confounder-adjusted non-linear association for live birth and β-carotene (p=0.03; q=0.05), which, in conjunction with the linear effect for β-carotene, led to overall 17% lower (RR=0.83; 95% CI=0.59-1.16), 9% lower (RR=0.91; 95% CI=0.54-1.52) , and 31 % higher (RR=1.31; 95% CI=0.67-2.56) likelihoods for a live birth per 1, 2, and 3 Z-score higher β-carotene concentrations, respectively. However, only the associations described in the live birth models remained statistically significant when adjusting for multiple comparisons using the false discovery rate.

To assess the impacts of our assumptions, we conducted sensitivity analyses. Supplemental Table IV presents the results of modified Poisson regression models simultaneously including multiple serum lipids and lipophilic micronutrient concentrations as predictors, adjusted for confounders as well as for the number of embryos transferred. The results were similar to those for the models without adjustment for the number of embryos transferred, although the association for β-cryptoxanthin with implantation was of borderline statistical significance (RR=0.84; 95% CI=0.69-1.01; p=0.07). Results were also similar when we adjusted the models for fertilization method (data not shown). Supplemental Table V presents the results of the main models limited to n=112 non-Asian participants. Results were similar, although less precise, than for the overall study population. However, the live birth association was stronger for γ-tocopherol (RR=1.51; 95% CI=1.03, 2.22) and weaker for α-tocopherol (RR=1.34; 95%CI=0.70, 2.56) and triglycerides (RR=0.57; 95% CI=0.25, 1.32) relative to the overall study population, suggesting that the effects may vary by race. Supplemental Table VI presents the results of modified Poisson regression models limited to n=144 with complete case data. Overall, the results were similar to those generated using multiple imputation. We also identified similar effects for serum lipid and lipophilic micronutrient concentrations on IVF outcomes when including n=180, irrespective of embryo transfer, in an “intention-to-treat” type analysis (Supplemental Table VII).

According to a post hoc power analysis (Supplemental Table VIII) our sample size was sufficient for detecting statistically significant associations between live birth and serum concentrations of HDL, triglycerides, α- and γ-tocopherols, and retinol. Moderate increases in sample size, between 2- and 6-fold, will be necessary to detect associations for live birth

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with serum phospholipids, β-cryptoxanthin, lutein, and lycopene at α=0.05. In contrast, much larger sample size increases of more than 100-fold would be necessary for detecting statistically significant associations between live birth and serum concentrations of LDL and α-carotene.

Discussion

The results of this prospective cohort study suggest that women with higher preconception serum α-tocopherol levels were more likely to experience a live birth from IVF than women with lower levels, and that women with higher triglyceride levels were less likely to have a live birth than women with lower levels. We also found a non-linear association between β-carotene levels and live birth. These results were adjusted for other serum lipids and lipophilic micronutrients, demographic and clinical confounders, and multiple comparisons, and were robust to sensitivity analyses. To our knowledge, this is the first study of preconception measurements of a comprehensive mixture of serum lipids and lipophilic micro nutrients simultaneously considered as predictors of clinical pregnancy outcomes from IVF.

Few previous observational studies have investigated the association between lipid and lipophilic micronutrient concentrations and clinical IVF outcomes. An earlier study of 25 women undergoing IVF (Palini et al. 2014) reported significantly higher pre-pregnancy (i.e., day of oocyte retrieval) mean plasma α-tocopherol and β-carotene concentrations among 8 women who achieved pregnancies (20.05 μmol/L and 0.66 μmol/L, respectively) compared to 15 women without pregnancy (16.98 μmol/L and 0.39 μmol/L, respectively). Although we did not detect associations for α-tocopherol or β-carotene in relation to implantation, our findings of an association between higher α-tocopherol and β-carotene and a higher likelihood of live birth are consistent with the overall pattern of previous associations found between α-tocopherol and β-carotene and number of oocytes retrieved, number of mature oocytes, and implantation (Palini et al. 2014). The discrepant results regarding implantation might be attributed to our adjustment for other lipids and lipophilic micronutrients as well as for confounding variables, and our diverse study population, comprised of approximately 30% Asian women. Moreover, our results are not consistent with our own prior findings that higher levels of FF HDL, δ-tocopherol, and γ-tocopherol were associated with better embryo quality (Browne et al. 2008, Browne et al. 2009, Kim et al. 2017a). Alternatively, the discrepancy may reflect the different lipid and micronutrient concentrations in serum and FF. A future analysis of FF lipid and lipophilic micronutrient concentrations in association with pregnancy and live birth will help to clarify this discrepancy.

Several clinical trials have reported on associations between lipophilic micronutrient supplementation in women and IVF endpoints, although with inconsistent results. A supplementation trial demonstrated significantly higher pregnancy rates from an administered daily dose of tocopherol in conjunction with vitamin D_3 in women with polycystic ovary syndrome (Fatemi et al. 2017). Moreover, supplementation of β-carotene and tocopherol was found to be associated with a shorter time to pregnancy in women treated for unexplained infertility (Ruder et al. 2014). However, in other studies, tocopherol supplementation was not found to be associated with implantation or ongoing pregnancy

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rates (Cicek et al. 2012), and similarly, no association was revealed between supplementation of multivitamins and minerals and oocyte quality or pregnancy rates in women undergoing IVF/ICSI (Youssef et al. 2015). Several systematic reviews have also concluded that tocopherol supplementation did not lower the risk of fetal loss or stillbirth (Rumbold et al. 2015), including in the presence of vitamin C (Polyzos et al. 2007, Rumbold et al. 2008) or vitamin A (Balogun et al. 2016). Our findings are consistent with positive associations reported for α-tocopherol and β-carotene and pregnancy in supplementation trials. However, given the overall inconsistency across studies, additional investigation is needed.

The mechanisms behind these associations between lipids and lipophilic micronutrients and reproductive outcomes are unknown; however, lipid accumulation in non-adipose tissues, or lipotoxicity, leading to mitochondrial dysfunction and reduced fecundability, may be a contributing factor (Wu et al. 2010). Furthermore, of eight recognized structural tocopherol isomers, α-tocopherol is the most potent and the only form of vitamin E recognized to meet human needs (Traber 2013), while the less potent γ-tocopherol form of vitamin E constitutes 70% of the tocopherol intake in the American diet (Swanson et al. 1999, Dietrich et al. 2006). However, α-tocopherol supplementation trials have demonstrated inverse correlations between serum γ- and δ-tocopherol concentrations and the more potent α-tocopherol isomer (Huang and Appel 2003, Gutierrez et al. 2009). This is likely due to binding competition for hepatic tocopherol transfer protein (Hosomi et al. 1997), resulting in preferential secretion of α-tocopherol into circulation (Traber 2013). Higher levels of α-tocopherol and lower levels of γ-tocopherol in this cohort, as compared to the general population, suggest compliance with clinician recommended micronutrient supplementation during the IVF cycle by means of a prenatal vitamin.

Our findings are limited by several factors. First, our study was insufficiently powered to detect associations for some lipids/lipophilic micronutrients with live birth. However, we achieved approximately 80% power to detect statistically significant associations with HDL, triglycerides, α- and γ-tocopherols, and retinol. The exponential increase in participant numbers needed to detect statistically significant associations for LDL and α-carotene suggests their implausibility in the source population. Our limited sample size also precluded a stratified assessment of associations according to race, although the results of our sensitivity analysis limited to non-Asian participants suggested the possibility for modification by race. A larger diverse study population will be necessary for more definitive results. Second, to limit our analysis to women ”at risk” for pregnancy and live birth, we excluded n=13 without embryo transfers, a potential source of bias (Messerlian and Gaskins 2017). However, we found similar results when including n=13 without embryo transfers in a sensitivity analysis. Second, we cannot rule out residual confounding from our imprecise assessment of cigarette smoking (i.e., ever vs. never), rather than using a biomarker for tobacco exposure, and use of estimated, rather than measured, LDL. The use of estimated LDL may also account in part for the large proportion of participants outside of age-specific clinical reference intervals, and variation from clinical reference intervals may reflect, in part, effects of COS (Bloom et al. 2014, Palini et al. 2014). Still, there were very few smokers in our cohort and the Friedewald equation for LDL estimation is accurate across a wide range of serum triglyceride levels (<400 mg/dL) (Burtis et al. 2013), encompassing the

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vast majority of our study participants (98.8%). Furthermore, we cannot rule out confounding by diet and supplement use, as well as other unconsidered lifestyle factors for which data were unfortunately unavailable. A future investigation incorporating dietary and lifestyle data will be necessary for more definitive results. Third, we were unable to incorporate paternal data into the analysis, which may also impact IVF outcomes, given that higher male cholesterol levels have been associated with reduced fecundability (Schisterman et al. 2014). Thus, a future "couples-based" investigation to simultaneously consider maternal and paternal lipids and lipophilic micronutrients is merited. Furthermore, prior studies have shown that HDL is increased at the time of oocyte retrieval (Brizzi et al. 2003) and concentrations of α-tocopherol, γ-tocopherol (Aurrekoetxea et al. 2010), and β-carotene decrease after COS (Palini et al. 2014), so additional investigation is needed to determine whether our findings can be extrapolated to pre-COS serum concentrations.

The generalizability of our results may also be limited. This cohort of women was referred to a single center for IVF (Buck Louis et al. 2005) and women undergoing IVF tend to be wealthier, more educated, and more likely to be non-Hispanic white or Asian compared to the general population (Katz et al. 2011, Datta et al. 2016). Furthermore, this cohort had a high proportion of Asian participants, who are known to have poorer IVF outcomes than their white counterparts (Langen et al. 2010) and distributions of some lipophilic micronutrients varied from those reported for similarly aged women in the general U.S. population.

Our findings are the first to report a higher likelihood for live birth after IVF among women with lower serum triglyceride and higher serum α-tocopherol and β-carotene concentrations, as part of a mixture of lipids and lipophilic micronutrients. While the mechanisms behind this association are unclear, our results suggest potential opportunities for clinical intervention. Serum lipid and lipophilic micronutrient data are readily available to clinicians treating infertile patients, and modification of constituents, if effective, might be achieved through supplementation or other non-invasive means. Still, the results of clinical supplementation trials that include tocopherols have been inconsistent regarding implantation and pregnancy maintenance, and supplementation is not without risks (Hovdenak and Haram 2012), so it should be considered as a potential intervention with caution.

In conclusion, while components of the mixture of lipids and lipophilic micronutrients were found to be associated with live birth outcomes following IVF in this exploratory analysis, a more definitive investigation with a larger number of participants is necessary to more fully evaluate the potential clinical implications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biography

Erica Jamro is a PhD student in Epidemiology at the University of Albany, State University of New York, where she also obtained her MS in Epidemiology in 2018. Her research interests include reproductive epidemiology and epidemiological methods.

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Key Message

A preconception mixture of serum lipids and lipophilic micronutrient concentrations appears to be important for live birth outcomes after IVF. These serum data are available to clinicians treating infertile patients, and modification of constituents, if effective, might be a potential target for non-invasive clinical interventions to improve live birth rates.

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TABLE I.

Distribution of demographic and clinical factors for women undergoing IVF

Participant Characteristics	n	Mean (SD) or %
Demographic Characteristics		
Age, years	167	37.2 (4.3)
BMI, kg/m^2	167	24.3 (4.6)
Race		
Not Asian	112	70.9%
Asian	46	29.1%
Smoking		
Never	143	88.8%
Ever	18	11.2%
Clinical Characteristics		
Primary infertility diagnosis		
Male factor / PGD	60	35.9%
Unexplained	45	27.0%
Female factor, non-DOR	34	20.4%
Female factor, DOR	28	16.8%
Stimulation protocol		
LDR	112	67.1%
Antagonist	42	25.2%
Flare	13	7.8%
Fertilization method		
ICSI	125	74.9%
Conventional	42	25.2%
Oocytes retrieved	167	11.9 (6.3)
Total embryos	167	6.2 (4.3)
Embryos transferred	167	2.6 (1.5)
Implantation		
No	76	45.5%
Yes	91	54.5%
Clinical Pregnancy		
No	105	62.9%
Yes	62	37.1%
Live Birth		
No	119	71.3%
Yes	48	28.7%

Abbreviations: BMI, body mass index; DOR, diminished ovarian reserve; ICSI, intracytoplasmic sperm injection; LDR, long down regulation; PGD, preimplantation genetic diagnosis

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TABLE II.

Distribution of serum lipid and lipophilic micronutrient concentrations for women undergoing IVF

	n[a]	Mean	SD	Min.	25th %tile	50th %tile	75th %tile	Max.
Phospholipids, mg/dL	154	210.80	33.44	137.00	190.00	208.50	227.50	314.00
HDL, mg/dL	154	55.84	13.05	30.10	46.66	56.20	63.71	90.61
LDL, mg/dL[b]	154	83.83	23.32	34.17	68.70	82.13	95.71	156.14
Triglycerides, mg/dL	154	113.56	65.64	35.92	75.12	95.66	128.42	419.73
α-Tocopherol, μg/mL	160	12.36	3.76	5.83	9.90	11.80	13.67	31.54
δ-Tocopherol, μg/mL	160	0.01	0.02	0.00	0.00	0.00	0.00	0.15
γ-Tocopherol, μg/mL	160	0.49	0.42	0.00	0.23	0.41	0.65	2.21
Retinol, μg/mL	160	0.50	0.11	0.24	0.43	0.51	0.56	1.06
β-Carotene, μg/mL	160	0.28	0.21	0.03	0.15	0.22	0.33	1.17
α-Carotene, μg/mL	160	0.02	0.03	0.00	0.01	0.02	0.03	0.32
β-Cryptoxanthin, μg/mL	160	0.13	0.11	0.005	0.06	0.10	0.17	0.68
Lutein, μg/mL	160	0.19	0.10	0.05	0.13	0.17	0.22	0.62
Lycopene, μg/mL	160	0.41	0.15	0.05	0.30	0.39	0.51	0.85

[a] Includes only women without missing values for lipids and lipophilic micronutrients.

[b] Estimated using Friedewald equation.

Abbreviations: HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; %tile, percentile

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TABLE III.

Adjusted risk ratios [95% CI] for the associations between serum lipid and lipophilic micronutrient concentrations (Z-scores) and IVF outcomes (n=167)[a]

	Implantation		Clinical Pregnancy		Live Birth	
	Risk Ratio [95% CI]	***P-value***	**Risk Ratio [95% CI]**	***P-value***	**Risk Ratio [95% CI]**	***P-value***
Phospholipids	1.09 [0.83, 1.42]	0.54	0.88 [0.59, 1.30]	0.51	1.10 [0.68, 1.78]	0.70
HDL	0.96 [0.75, 1.22]	0.73	1.002 [0.71, 1.40]	0.99	0.68 [0.45, 1.03]	0.07
LDL[b]	1.10 [0.91, 1.33]	0.31	1.09 [0.78, 1.51]	0.61	1.05 [0.73, 1.51]	0.78
Triglycerides	0.996 [0.78, 1.27]	0.98	0.76 [0.53, 1.09]	0.13	**0.54 [0.33, 0.90]**	**0.02**[c]
α-Tocopherol	1.03 [0.83, 1.28]	0.79	1.14 [0.75, 1.72]	0.54	**1.61 [1.11, 2.36]**	**0.01**[c]
δ-Tocopherol	1.01 [0.91, 1.13]	0.80	1.03 [0.91, 1.16]	0.62	1.12 [0.97, 1.30]	0.13
γ-Tocopherol	1.09 [0.90, 1.32]	0.37	1.08 [0.74, 1.58]	0.69	1.29 [0.95, 1.74]	0.10
γ-Tocopherol^2[d]	-	-	1.07 [0.92, 1.25]	0.39	-	-
Retinol	0.96 [0.81, 1.15]	0.68	1.03 [0.79, 1.34]	0.83	0.89 [0.65, 1.21]	0.44
β-Carotene	1.05 [0.88, 1.25]	0.62	0.74 [0.52, 1.06]	0.10	0.72 [0.47, 1.12]	0.14
β-Carotene^2[d]	-	-	**1.14 [1.03, 1.26]**	**0.01**	**1.15 [1.02, 1.30]**	**0.03**[c]
α-Carotene	0.92 [0.77, 1.10]	0.36	0.92 [0.72, 1.16]	0.48	0.98 [0.74, 1.30]	0.91
β-Cryptoxanthin	**0.82 [0.68, 0.99]**	**0.04**	0.96 [0.76, 1.20]	0.70	1.09 [0.86, 1.40]	0.47
Lutein	0.98 [0.86, 1.13]	0.81	0.90 [0.72, 1.13]	0.38	0.87 [0.67, 1.14]	0.31
Lycopene	0.94 [0.81, 1.09]	0.40	0.80 [0.64, 1.003]	0.05	0.87 [0.66, 1.14]	0.30

NOTE: All lipids and lipophilic micronutrients simultaneously included as predictors in modified Poisson regression model models of IVF outcomes; values imputed for n=23 women with missing data for some variables; associations with $p < 0.05$ in bold typeface.

[a]Adjusted for mother's age (years), body mass index (kg/m^2), race (Asian vs. non-Asian), smoking status (ever vs. never), primary infertility diagnosis (female non-diminished ovarian reserve (DOR) vs. female DOR vs. male or preimplantation genetic diagnosis vs. undetermined), and ovarian stimulation protocol (antagonist vs. clomid flare or microdose flare vs. long luteal or demi-halt or very low dose leuprolide acetate)

[b]Estimated using Friedewald equation.

[c]False discovery rate Q-value < 0.05.

[d]Quadratic term indicates a non-linear association with the outcome.

Abbreviations: HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol