Clomiphene citrate dose and reproductive and perinatal outcomes in fresh autologous in vitro fertilization cycles, United States, 2004-2021

Michael Davies, PhD, MPH[1] Sheree Boulet, DrPH, MPH,[2]
[1]Robinson Research Institute and School of Biomedicine, Adelaide University, [2]Department of Obstetrics and Gynecology, Boston University Chobanian & Avedisian School of Medicine
michael.davies@adelaide.edu.au sheree.boulet@bmc.org

OBJECTIVE

Having demonstrated that clomiphene citrate (CC) is related to multiple pregnancy, prematurity, birth defects & perinatal death (NEJM, PLOS One, JCEM), and recapitulated these observations experimentally in a dose-dependent way within a murine model (Endocrinology), we sought to confirm a cumulative dose-response relationship of clomiphene citrate (CC) across courses on the risk for fetal death among fresh autologous IVF cycles.

BACKGROUND

- Clomiphene citrate (CC) was approved in 1967 and became a WHO first line infertility therapy & also as part of in vitro fertilization (IVF) stimulation protocols to promote follicular development.
- CC use frequently precedes IVF as an effective first line treatment, but often without formal epidemiological monitoring.
- CC use and dose increase the risk of ovarian hyperstimulation syndrome, multiple pregnancy, miscarriage, prematurity, birth defects, and perinatal death.
- However, within an IVF cycle, there is limited evidence examining the association between cumulative dose and adverse outcomes.
- Demonstrating a dose response relationship between CC and fetal death within a clinical infertility population greatly reduces the risk of confounding by indication, whilst replicating our published murine model, and extending our human studies.

PARTICIPANTS AND METHODS

- Data from CDC's National Assisted Reproductive Technology Surveillance System were restricted to fresh, autologous IVF cycles performed between 2004 and 2021 where CC was used for ovulation induction

Exposure

- Four categories of total CC dosage per cycle:
  - <500mg
  - 500-749mg
  - 750-999mg
  - ≥1000mg

Outcomes

- Biochemical pregnancy, intrauterine pregnancy, spontaneous abortion, stillbirth, live birth, multiple birth, and preterm delivery (<37 weeks gestation)

Analysis

- Linear regression to test for trends in annual mean CC dose
- Multiple imputation to derive values for missing race & ethnicity and body mass index (BMI)
- Robust Poisson regression with generalized estimating equations to account for clustering by clinic
  - Estimated adjusted risk ratios (aRR) and 95% confidence intervals (CI) for the association between CC dose and outcomes
  - Models adjusted for age at cycle start, parity, number of prior IVF cycles, infertility diagnosis, race and ethnicity (imputed), and BMI (imputed)
  - Pooled parameter estimates and standard errors over 20 imputed datasets

Study population

- There were 1,698,813 fresh cycles in 2000-2021; 3.1% reported information on CC.
- After exclusions, the final sample included 21,004 fresh, autologous IVF transfer cycles

RESULTS

Trends in mean total clomiphene dosage among fresh autologous IVF cycles, 2004-2021

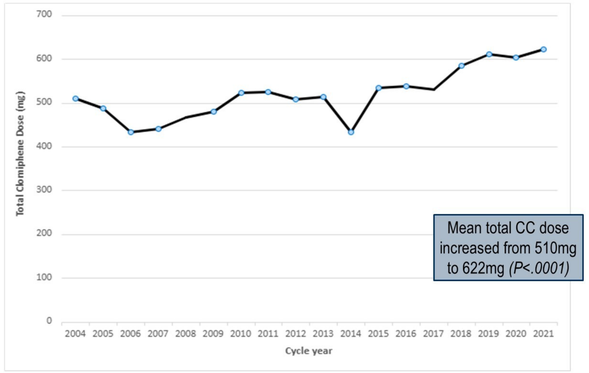

Table 1. ***Association between categories of total clomiphene dosage and perinatal outcomes in 21,004 fresh, autologous in vitro fertilization embryo transfer cycles (2004-2021)***

	<500mg N=4,476		500-749mg N=14,241		750-999mg N=1,517		≥1000mg N=770	
	%	aRR	%	aRR (95%CI)	%	aRR (95%CI)	%	aRR (95%CI)
Biochemical pregnancy	6.8	Ref	7.0	1.00 (0.87-1.13)	6.7	0.97 (0.77-1.21)	6.9	0.98 (0.77-1.31)
Intrauterine pregnancy	25.1	Ref	27.3	1.06 (1.00-1.13)	29.0	1.06 (0.97-1.17)	28.6	1.05 (0.93-1.18)
Spontaneous abortion	10.3	Ref	11.8	1.12 (1.02-1.25)	14.4	1.38 (1.18-1.62)	12.5	1.18 (0.95-1.47)
Stillbirth	0.2	Ref	0.3	1.57 (0.74-3.34)	0.4	1.99 (0.74-5.89)	0.7	3.31 (0.88-12.40)
Live birth	18.6	Ref	19.8	1.03 (0.96-1.10)	21.4	1.02 (0.91-1.14)	22.5	1.08 (0.94-1.23)

Table 2. ***Association between categories of total clomiphene dosage and perinatal outcomes in 4,154 fresh, autologous in vitro fertilization embryo transfer cycles (2004-2021)***

	<500mg N=834		500-749mg N=2,823		750-999mg N=324		≥1000mg N=173	
	%		%	aRR (95%CI)	%	aRR (95%CI)	%	aRR (95%CI)
Multiple birth	13.2	Ref	17.7	1.35 (1.12-1.64)	21.3	1.55 (1.18-2.04)	27.2	1.88 (1.39-2.54)
Preterm delivery	17.2	Ref	19.7	1.17 (0.98-1.38)	19.2	1.13 (0.86-1.48)	20.2	1.15 (0.82-1.61)
Preterm delivery (singletons)	11.9	Ref	10.7	0.91 (0.71-1.15)	11.8	1.01 (0.68-1.50)	15.9	1.36 (0.86-2.14)

LIMITATIONS

- Restricted to fresh cycles
- Could not evaluate neonatal deaths
- Small sample size for some outcomes
- Unmeasured confounding
- CC use observed here is within IVF clinics, whereas much use is outside the monitoring systems of IVF registries.

MAIN RESULTS

- The mean total CC dose in fresh autologous IVF cycles increased during 2004-2021.
- This indicates a secular change in either the aggressiveness of the treatment strategy, delayed progression to IVF, or diminished patient responsiveness related to factors such as BMI or age.
- There was a monotonic dose-relationship of CC category ≥500mg with the risk for spontaneous abortion, stillbirth, and multiple birth.
- However, the chance of a live birth did not increase in the same manner, indicating that there is a plateau effect of cumulative dose and risk vs benefit.

CONCLUSIONS

- As CC is a first line treatment for anovulatory infertility globally, it is imperative to reinforce the importance of complying with the manufacturer safety sheet to avoid fetal exposure, or excess dose, and to conduct further results on the minimal effective dose, and identify the source of inter-individual variability in effective dose.
- CC may contribute to adverse outcomes by inducing a thinner endometrium, which results in impaired vascularization, poor implantation, fetal development and potential fetal arrest.
- CC also disrupts cholesterol metabolism in the developing embryo, thereby interfering with gene expression essential for normal development

CONTACT INFORMATION

Sheree Boulet, DrPH, MPH
Department of Obstetrics and Gynecology Boston University Chobanian & Avedisian School of Medicine
Boston Medical Center, Boston, MA
sheree.boulet@bmc.org

Michael Davies, PhD, MPH
Robinson Research Institute and School of Biomedicine Adelaide University, Adelaide, SA, Australia
michael.davies@adelaide.edu.au

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Conflicts

The authors have no conflicts to declare

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