

Effects of Bisphenol A on Female Reproduction

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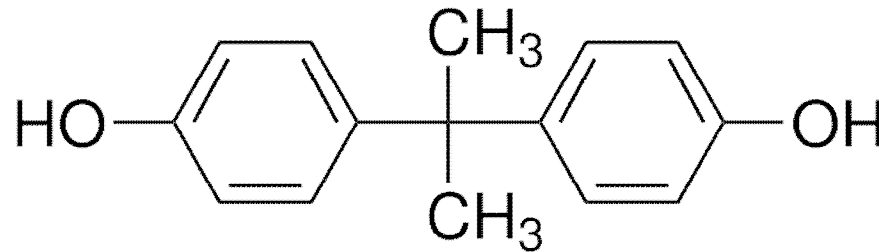
Overview

- Background
 - Bisphenol A (BPA)
 - Ovary
- Effects of pre-natal BPA exposure on the ovary and female reproductive system (F1)
 - Ovarian development and fertility
- Transgenerational effects of pre-natal BPA exposure on the ovary and female reproductive system (F2 and F3)
- Conclusions

What is Bisphenol A?



Bisphenol A (BPA)

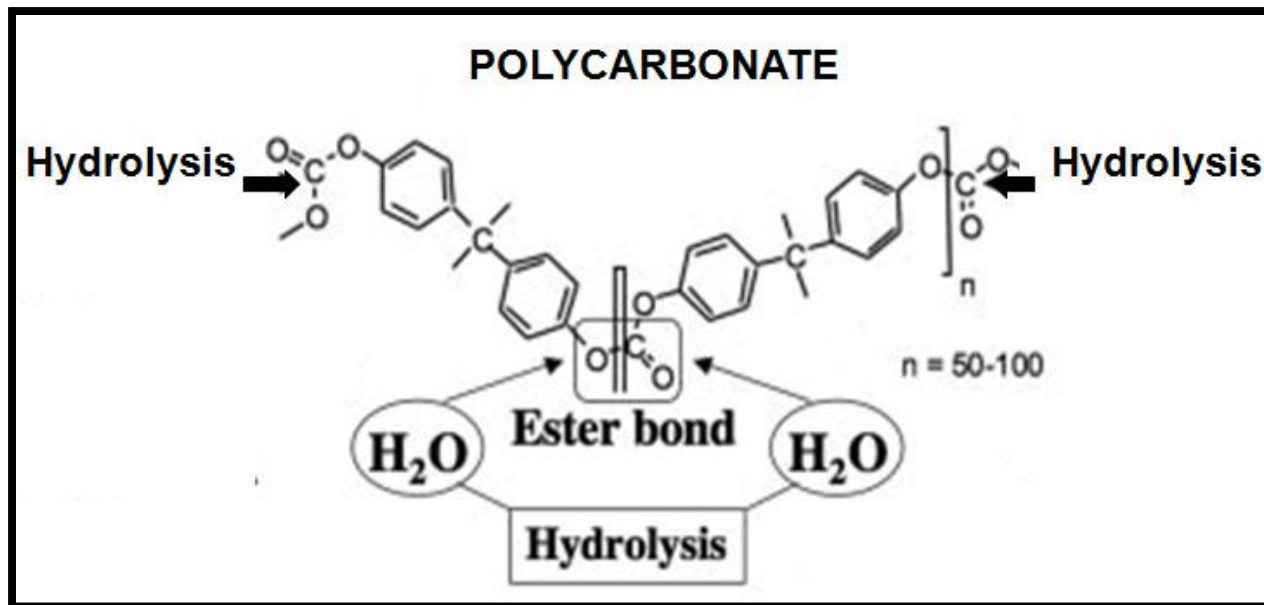


- BPA was originally synthesized in 1891 and intended for use as a chemical estrogen to help prevent miscarriage
- Diethylstilbestrol (DES) was a more potent estrogen and used instead of BPA
- BPA became widely used by manufacturers of polycarbonate plastics

Why the concern?



BPA Leaches Out of Plastics



BPA Enters the Body

- BPA is found in 95% of human urine samples, indicating nearly constant exposure to BPA
- BPA can rapidly cross the placenta and enter fetal organs in animal models
- BPA has been detected in the blood, serum, urine, liver, placenta, umbilical cord blood, and amniotic fluid in humans
- BPA has been detected in the ovary, particularly in follicular fluids

Pre-natal BPA Exposure Affects Reproduction

- Altered cyclicity
- Impaired ovulation in adult life
- Premature breast development
- Early puberty onset
- Abnormal chromosomes in oocytes

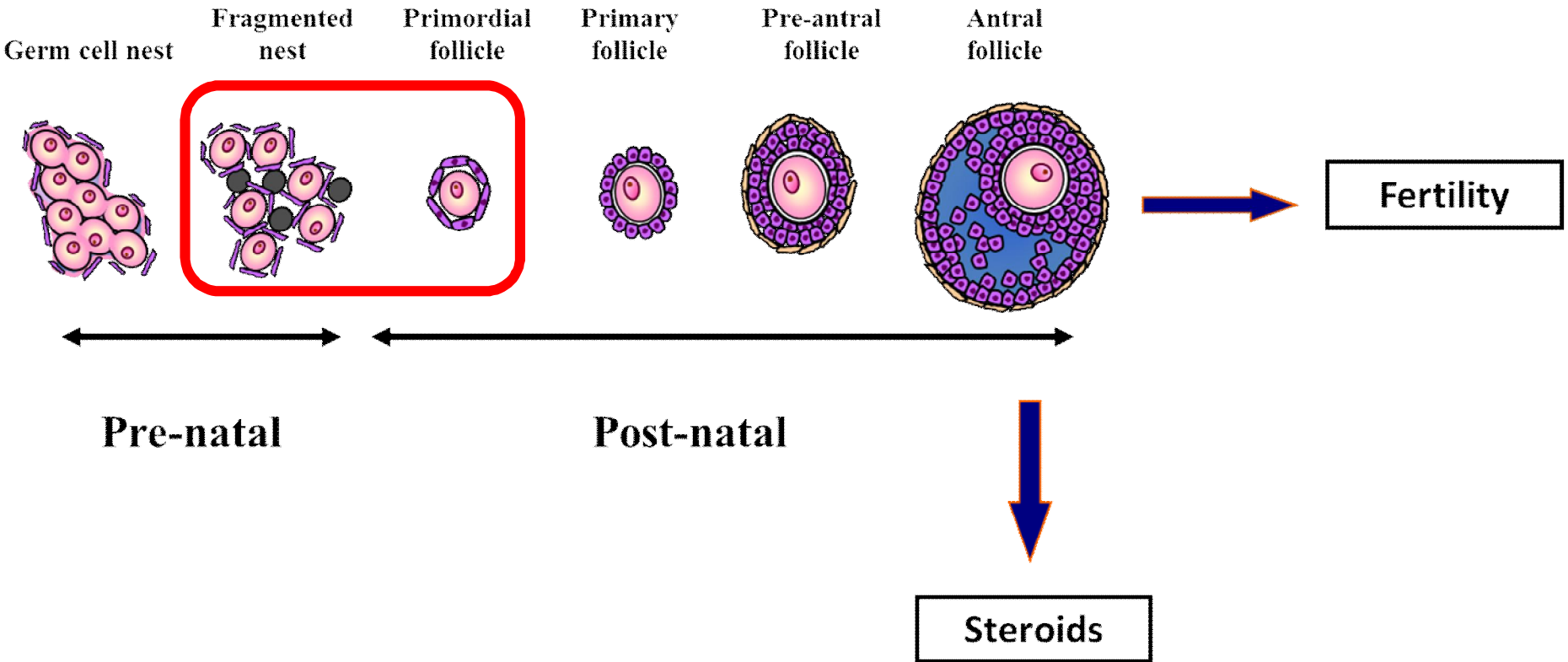
What other effects does pre-natal BPA exposure have on the ovary?



Functions of the Ovary

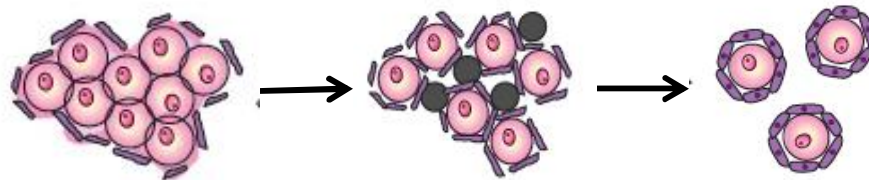
- Ovulation (oocytes)
 - Fertility
- Synthesize and secrete hormones
 - Development of ova
 - Implantation
 - Menstrual/estrous cyclicity
 - Maintenance of the reproductive tract
 - Fertility
 - Female health (cardiovascular, brain, bones)

Folliculogenesis

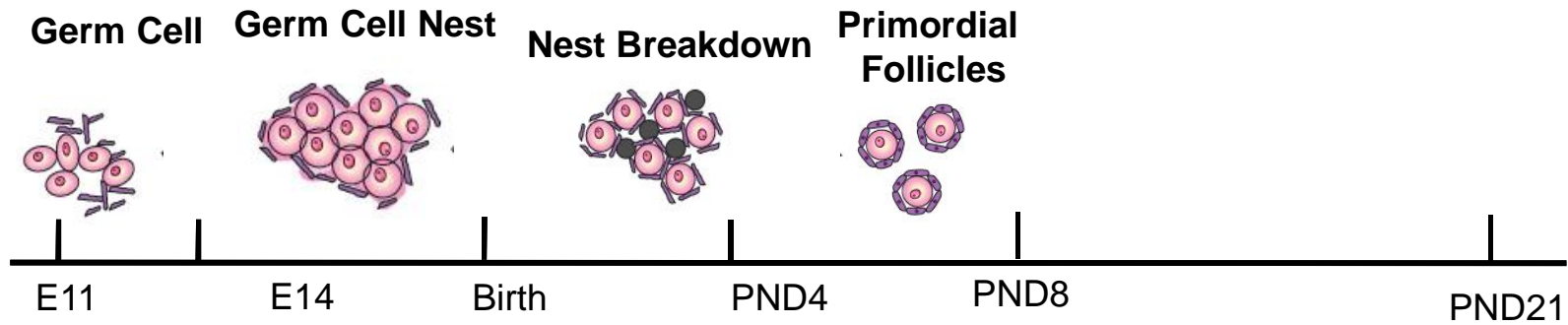


Hypothesis

Pre-natal BPA exposure affects germ cell nest breakdown, reducing the number of primordial follicles at birth



Experimental Design



 **Tissue collections**

Oral dosing (F0)
Tocopherol stripped corn oil (vehicle control)
BPA 0.5, 20, and 50 $\mu\text{g}/\text{kg}/\text{day}$

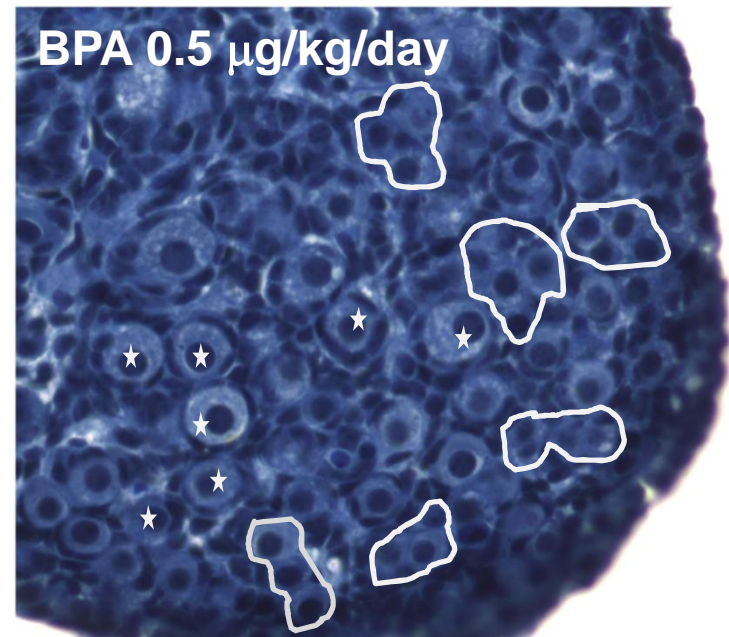
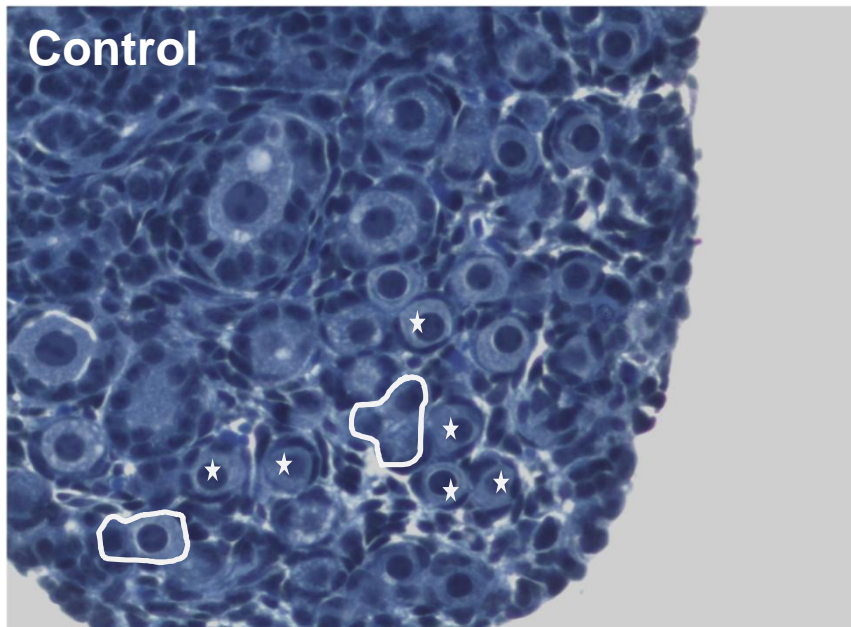
Ovaries (PND4)
histological evaluation of germ cell
nests and primordial follicles

Fertility Tests (3, 6, and 9 months)
breeding studies

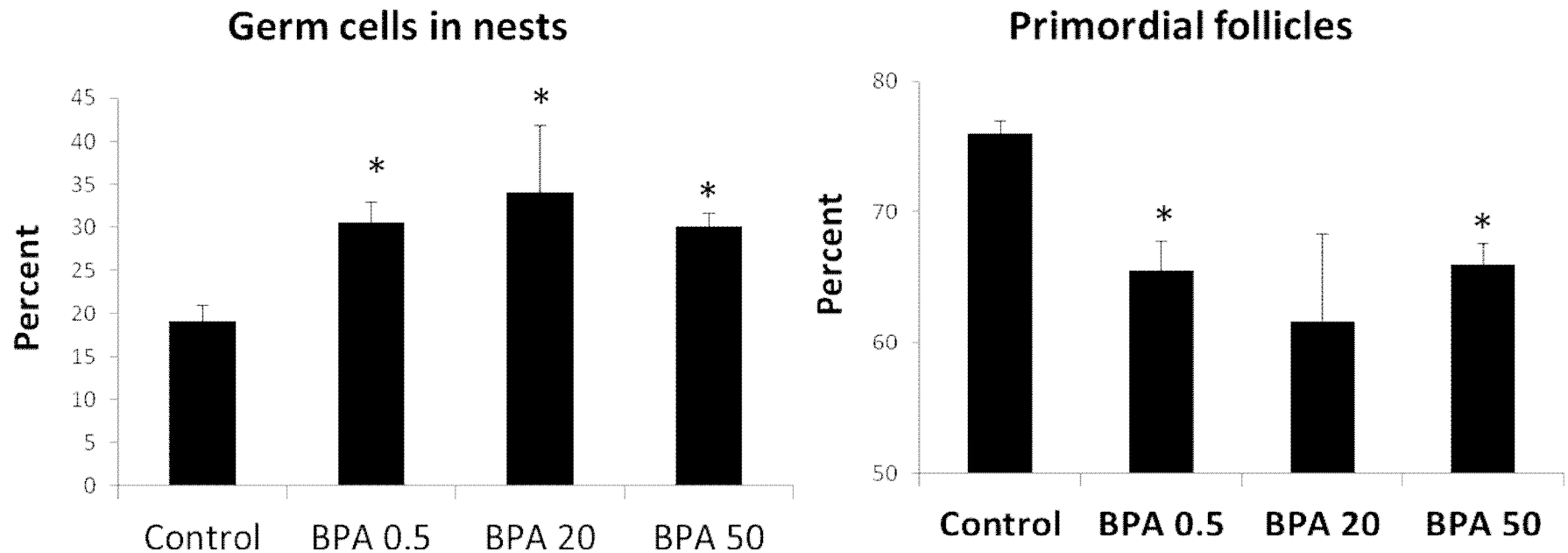
N=8 dams/treatment

BPA Inhibits Germ Cell Nest Breakdown (F1)

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BPA Inhibits Germ Cell Nest Breakdown (F1)



What are the consequences of pre-natal BPA exposure on fertility in later life?



Effect of BPA on F1 Fertility (3 months)

treatment	# breeding pairs	# with fertility problems	# of pups /litter	% dead pups
Control	9	0	10.4 ± 0.9	3.4 ± 1.9
BPA 0.5	7	<u>1</u>	10.2 ± 0.4	<u>9.9 ± 2.9</u>
BPA 20	7	0	9.6 ± 0.7	1.7 ± 1.7
BPA 50	11	<u>2</u>	10.4 ± 0.5	2.7 ± 1.4

Effect of BPA on F1 Fertility (6 months)

treatment	# breeding pairs	# with fertility problems	# of pups /litter	% dead pups
Control	9	0	10.1 ± 0.4	7.2 ± 3.2
BPA 0.5	6	<u>1</u>	10.2 ± 0.6	<u>28.2 ± 12.1</u>
BPA 20	7	<u>1</u>	8.6 ± 2.1	<u>30.7 ± 12.4</u>
BPA 50	11	<u>3</u>	<u>8.4 ± 0.4</u>	<u>21.2 ± 6.3</u>

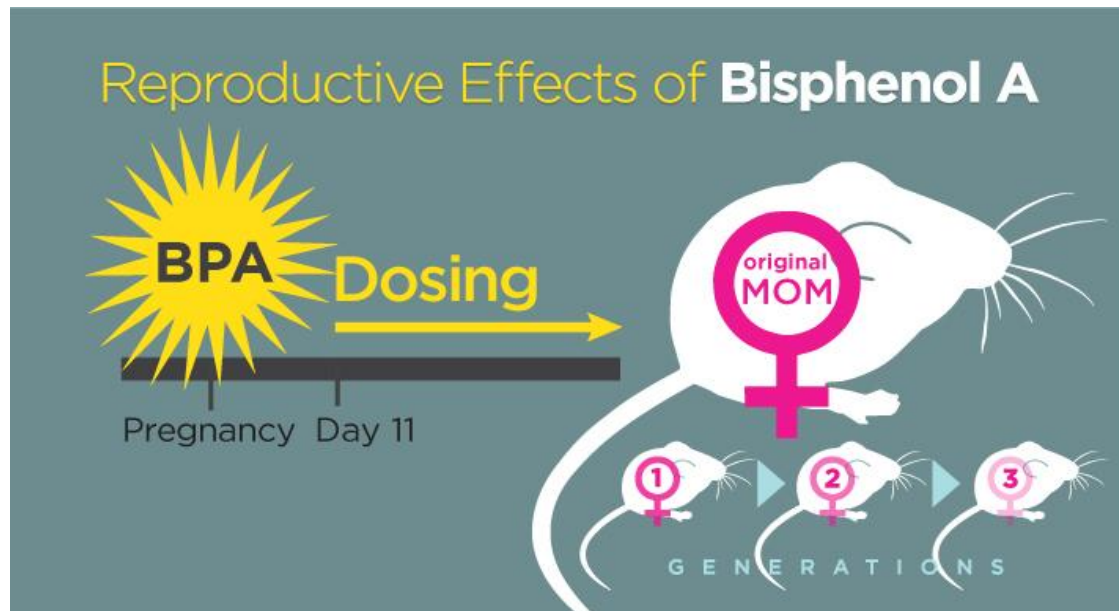
Effect of BPA on F1 Fertility (9 months)

Treatment	# breeding pairs	# with fertility problems	# of pups /litter	% dead pups
Control	9	2	6.9 ± 0.8	5.5
BPA 0.5	5	<u>5</u>	No live pups	<u>100</u>
BPA 20	6	<u>2</u>	6 ± 1.3	0
BPA 50	11	<u>6</u>	7.0 ± 0.9	<u>26.2 ± 14.2</u>

BPA-Induced Fertility Problems

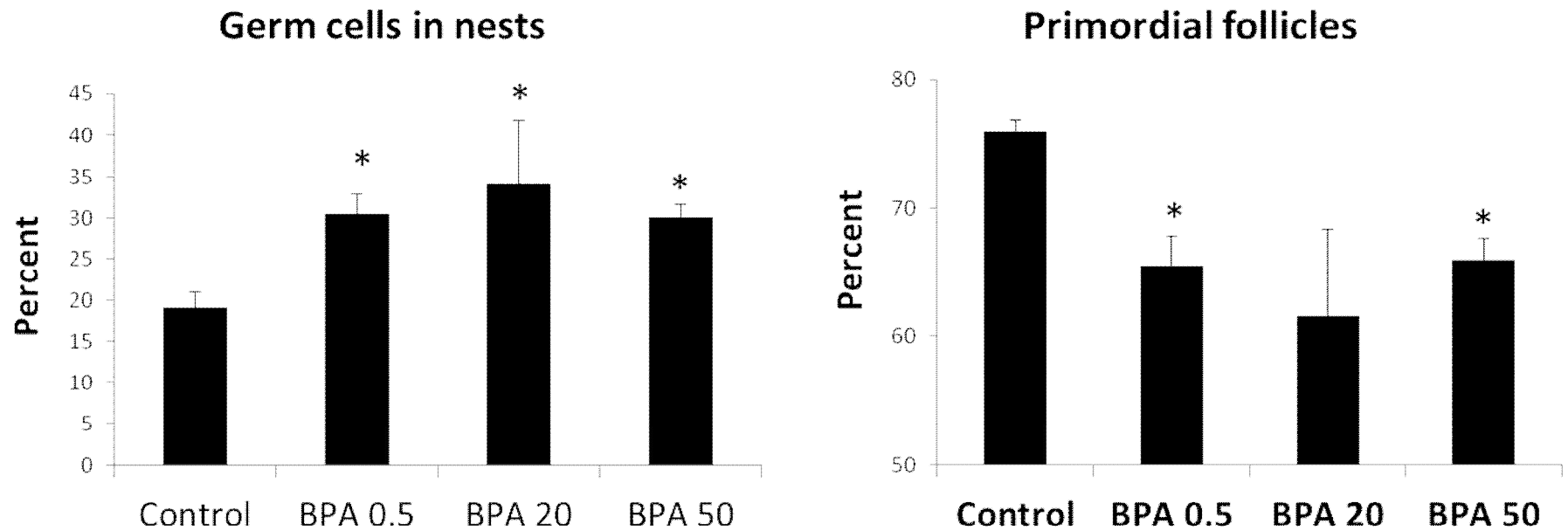
Type of infertility	Control	BPA 0.5	BPA 20	BPA 50
Ovulation problem	0	1 (3 month) 2 (9 month)	1 (9 month)	0
Mid-gestation problem	2 (9 month)	1 (6 month) 2 (9 month)	1 (9 month)	2 (3 month) 1 (6 month) 6 (9 month)
Late-gestation problem	0	1 (9 month)	2 (6 month)	2 (6 month)

Are these effects of BPA exposure transgenerational?

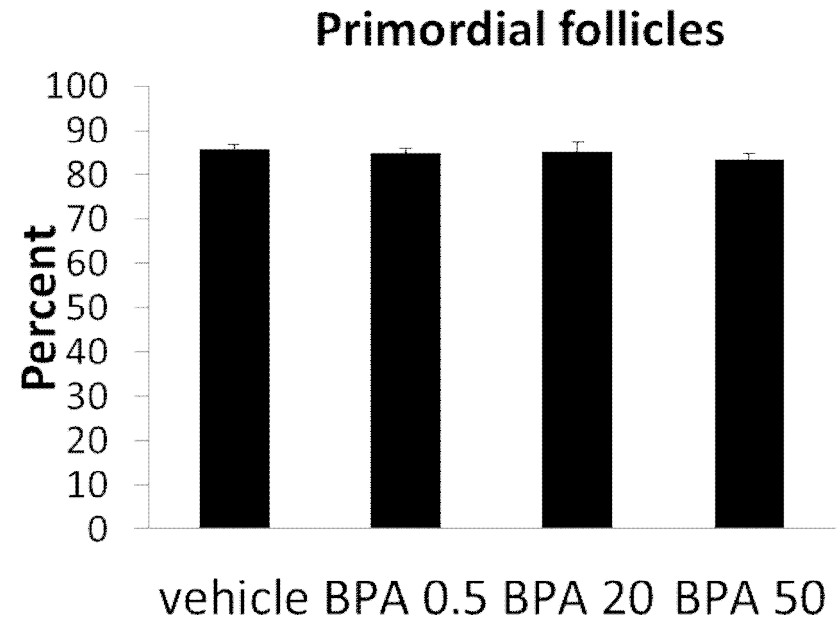
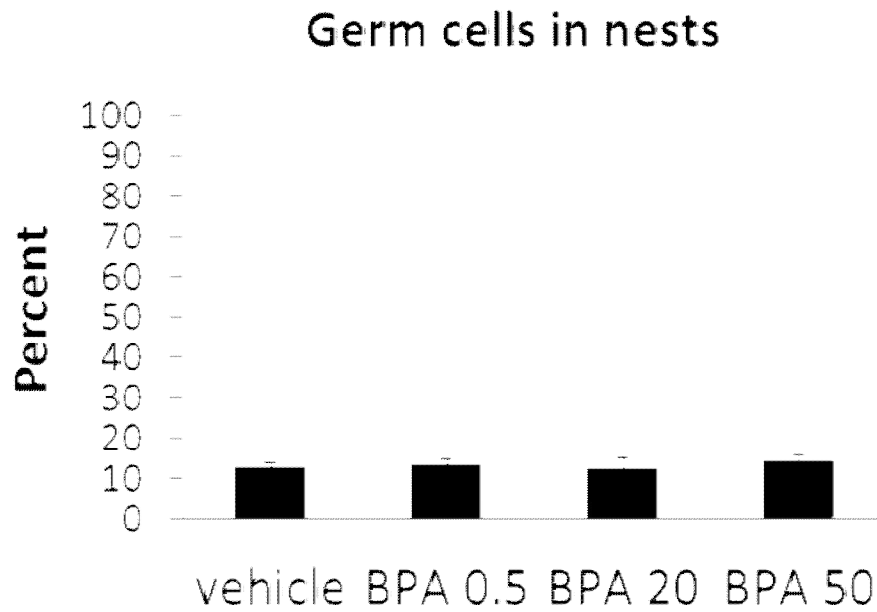


Germ cell nest breakdown
Female fertility

BPA Inhibits Germ Cell Nest Breakdown (F1)

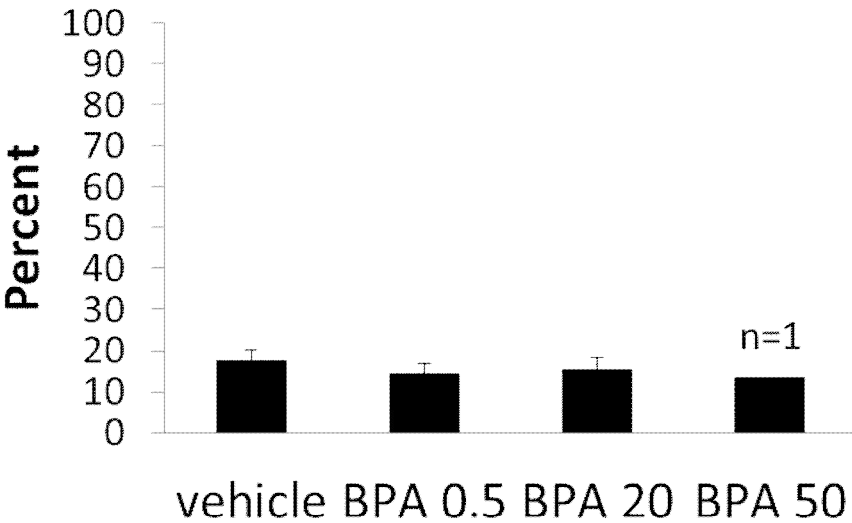


BPA Exposure and Germ Cell Nest Breakdown (F2)

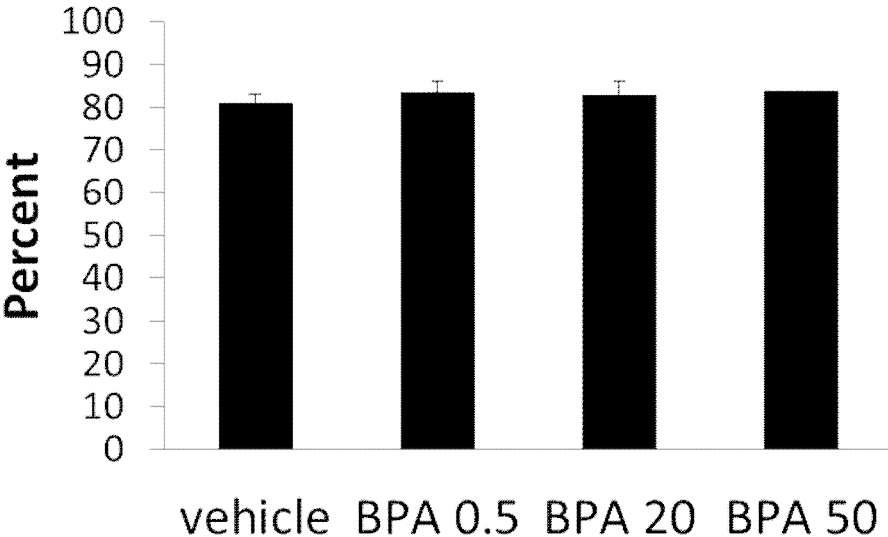


BPA Exposure and Germ Cell Nest Breakdown (F3)

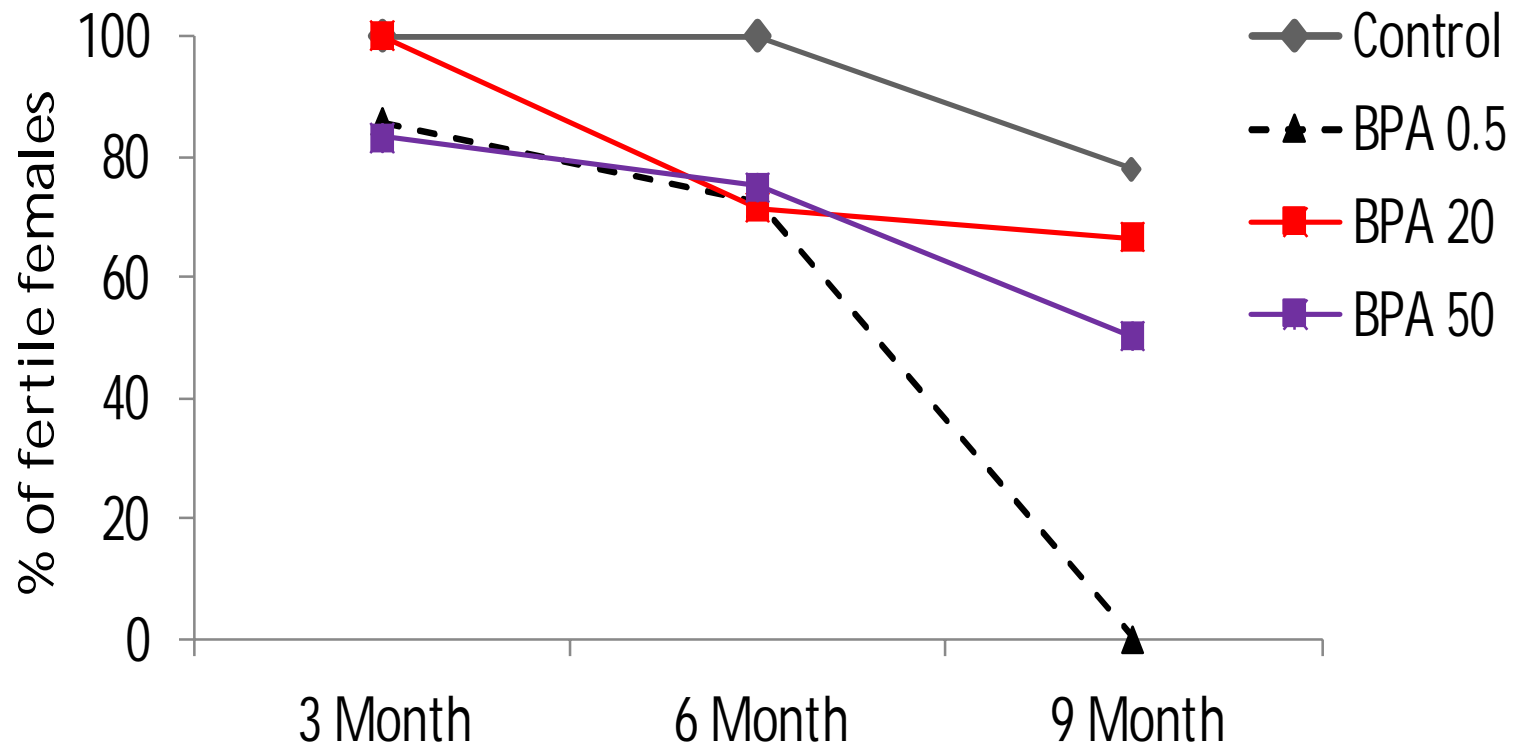
Germ cells in nests



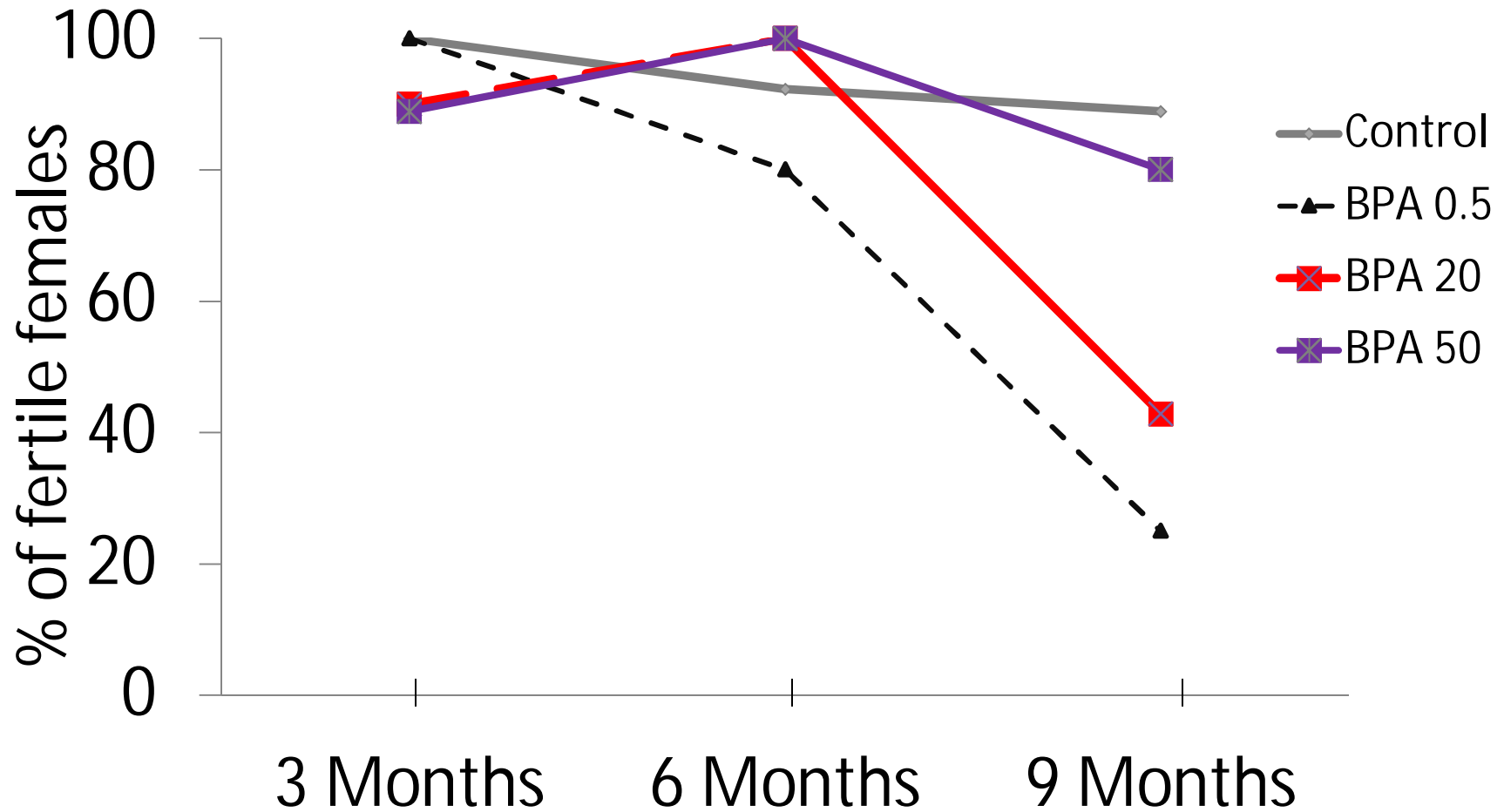
Primordial follicles



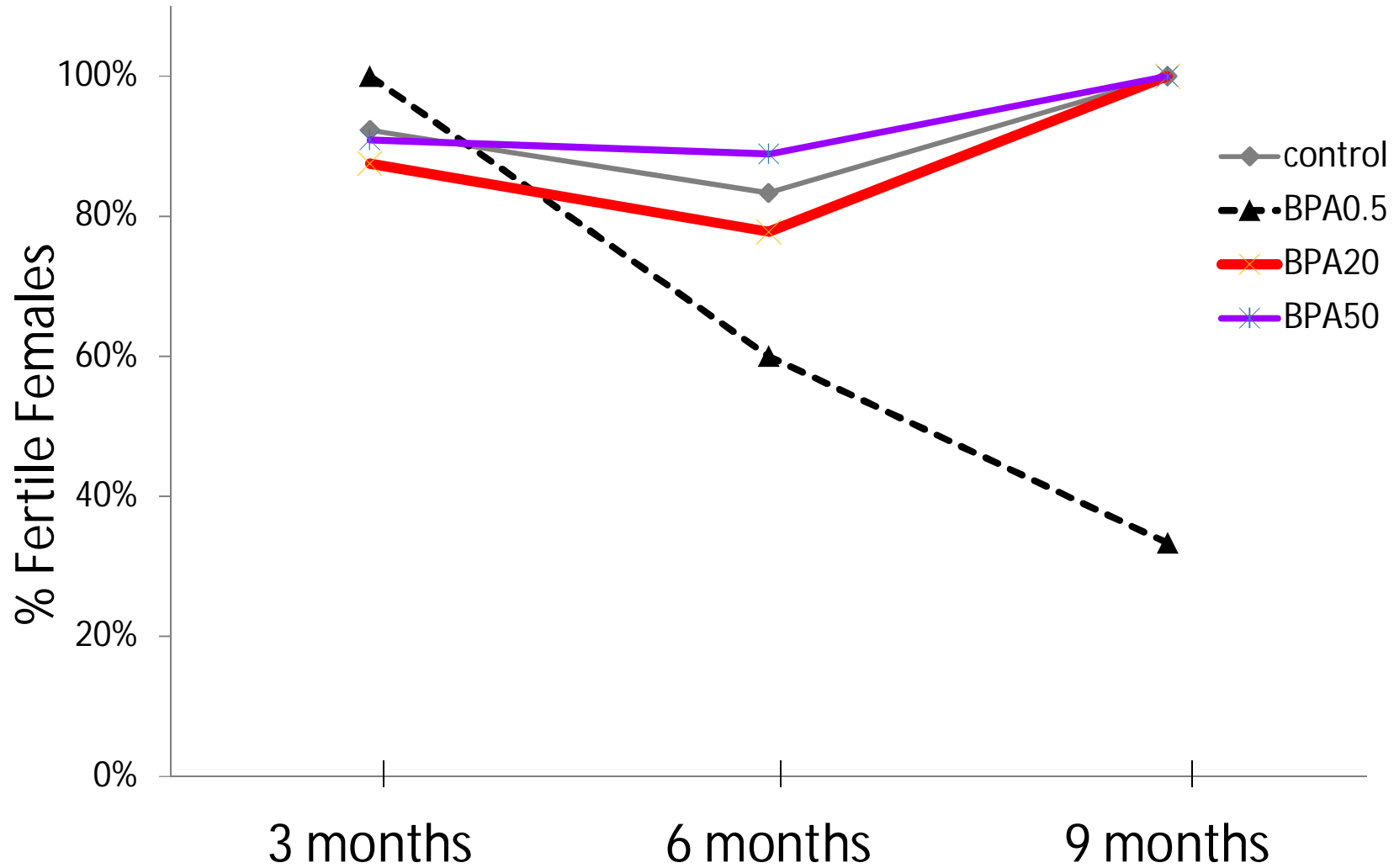
Effect of BPA on Fertility Over Time (F1)



Effect of BPA on Fertility Over Time (F2)



Effect of BPA on Fertility Over Time (F3)



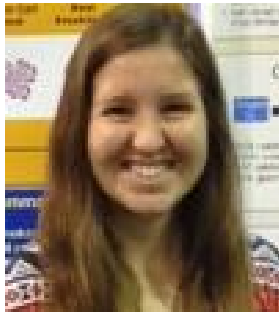
Summary

- Pre-natal BPA exposure:
 - Blocks germ cell nest breakdown (F1)
 - Reduces female fertility (F1, F2, and F3)
 - reduces ovulation
 - miscarriage
 - dead pups
- Some effects of pre-natal BPA exposure may get worse with age and persist in future generations (F1, F2, F3)

Conclusions

- Pre-natal BPA exposure inhibits germ cell nest breakdown, but this effect of BPA is not transgenerational
- Pre-natal BPA exposure reduces fertility in a transgenerational manner, but we do not know the mechanism underlying this effect yet

Acknowledgments



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