

Prenatal Smoke-Exposure is Associated with Increased Anogenital Distance in Female Infants

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INTRODUCTION AND OBJECTIVES:

Smoking is still quite common among pregnant women despite the known harmful effects. Cigarette contains more than 4,000 toxins and is suspected of having endocrine-disrupting properties. Maternal smoking during pregnancy may affect the intrauterine hormonal environment and this early fetal exposure may cause multiple adverse effects on offspring reproductive development. Anogenital distance (AGD) is being used to estimate the adverse effects of intrauterine exposure of endocrine disruptors. AGD is an important biomarker of fetal androgen exposure and intrauterine masculinization. It is known that AGD increases with androgenic exposure and reduces with antiandrogenic exposure.

There is limited number of studies examining whether AGD is affected by prenatal smoke-exposure. The aim of this prospective case control study is to investigate the effects of maternal smoking during pregnancy on newborn infants' AGD.

METHODS:

Fifty-six female and 64 male newborn infants from mothers who smoked during pregnancy were included in this study. The control group for each sex was selected from infants whose mothers had no active or passive (in either the household or the workplace) smoke exposure before or during pregnancy. Questionnaire data on maternal demographic characteristics and information about cigarette use were collected.

We assessed genital anthropometry which included AGD for both male and female neonates, and stretched penile length (SPL), penile girth for males within the first 48 hours after birth.

In boys, AGD was measured from anus to;

A) posterior insertion of the penis (AGDapp)

B) cephalad insertion of the penis (AGDap)

C) scrotum (AGDas)

In girls, AGD was measured from anus to;

A) posterior insertion of the clitoris (AGDapc)

B) the top of the clitoris (AGDac)

C) base of the posterior fourchette (AGDaf)

AGDapp/apc were also normalized according to birthweight (AGD/weight in grams), length (AGD/height in millimeters), and ponderal index (PI) [AGD/(weight in grams/height in cubic centimeters)]. Anogenital index (AGI) was calculated by dividing the AGDapp/apc by cube root of birthweight.

Table 1: Characteristics of maternal and infant, comparison of infant's AGD measurements

| | Female Infants | | | Male Infants | | |
|---------------------------------------|--|--|--------|--|--|--------|
| | Control Group (n=56) (mean±SD)(median) | Smoke-exposed Group (n=56) (mean±SD)(median) | p | Control Group (n=64) (mean±SD)(median) | Smoke-exposed Group (n=64) (mean±SD)(median) | p |
| Maternal Characteristics | | | | | | |
| Age (years) | 27.9±5.7 | 29.8±5.7 | 0.09* | 27 (18-42) | 25 (15-47) | 0.04* |
| Prepregnancy weight (kg) | 59 (40-85) | 63.5 (42-100) | 0.15** | 60 (4-101) | 60.5 (41-101) | 0.90** |
| Prepregnancy BMI (kg/m ³) | 22.6 (17-34.5) | 23.7 (16.4-35.6) | 0.44** | 22.7 (17.4-39.1) | 23.3 (14.4-41.5) | 0.65** |
| Weight at delivery (kg) | 74 (56-102) | 75 (56-110) | 0.60** | 73.5 (51-103) | 75 (50-113) | 0.25** |
| BMI at delivery (kg/m ²) | 28.6 (21.1-35.9) | 28.4 (22.3-38.1) | 0.64** | 27.2 (20.4-40.2) | 28.1(19.3-46.4) | 0.29** |
| Infants Characteristics | | | | | | |
| Weeks of gestation | 39 (38-41) | 39 (38-41) | 0.57** | 39 (38-42) | 39 (39-41) | 0.08** |
| Weight (g) | 3343±398 | 3179±395 | 0.03* | 3403±374 | 3318±411 | 0.22* |
| Height (cm) | 50 (45-53) | 50 (45-54) | 0.54** | 51 (40-54) | 50 (45-54) | 0.04** |
| Head circumference(cm) | 35 (32-37) | 35 (31-48) | 0.16** | 35 (33-37) | 35 (31.5-37.5) | 0.01** |
| Ponderal index (g/cm ³) | 2.67±0.26 | 2.57±0.22 | 0.02* | 2.63 (2-4.45) | 2.63 (2.17-3.20) | 0.62** |
| AGD measures | | | | | | |
| AGD (apc/app) (mm) | 43.3±6.8 | 44.1±7.3 | 0.54* | 54.2±4.3 | 54.2±7.6 | 0.95* |
| AGD (af/as) (mm) | 20 (10-24) | 18 (10-32) | 0.34** | 32 (20-45) | 31 (11-52) | 0.52** |
| AGD (ac/ap) (mm) | 50 (40-64) | 50 (35-63) | 0.88** | 60.5 (48-70) | 60 (30-85) | 0.34** |
| AGD indeksi (cm/kg ³) | 2.91 (1.95-4.02) | 3.11 (1.53-3.86) | 0.05** | 3.61±0.27 | 3.64±0.47 | 0.63* |
| AGD (apc/app)/weight | 13.1±2.2 | 14±2.5 | 0.03* | 16±1.8 | 16.5±2.4 | 0.26* |
| AGD (apc/app)/height | 0.86 (0.56-1.22) | 0.91 (0.45-1.16) | 0.17** | 1.07±0.09 | 1.08±0.14 | 0.66* |
| AGD (apc/app)/Ponderal index | 16.2±2.6 | 17.2±3 | 0.07* | 20.7±2.2 | 20.7±3 | 0.95* |
| Stretched penile length (mm) | - | - | - | 35.7±4.9 | 34.9±5.3 | 0.39* |
| Penile girth (mm) | - | - | - | 12 (10-14) | 12 (10-14) | 0.06** |

*Student T-test - Mean ± SD

**Mann-Whitney U test - Median (min-max)

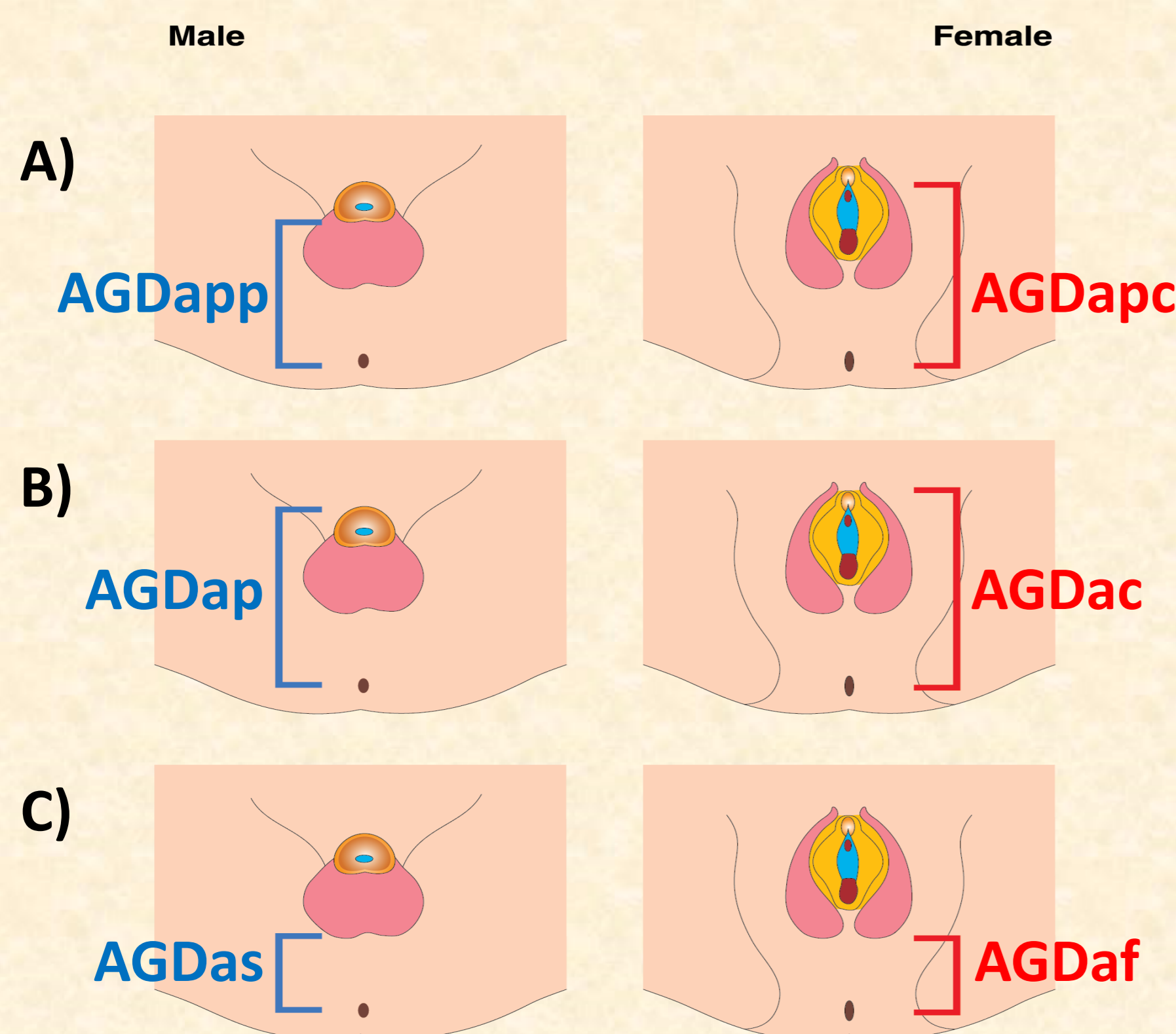
Table 2: Correlations between characteristics of maternal cigarette use and AGD measurements of infants

| Variables | AGD (apc/app) | | AGD (af/as) | | AGD (ac/ap) | | AGD (apc/app)/weight | | AGD (apc/app)/height | | AGD (apc/app)/PI | | AGD index | SPL | penile girth | |
|---|---------------|-------|-------------|-------|-------------|-------|----------------------|-------|----------------------|-------|------------------|-------|-----------|-------|--------------|-------|
| | F | M | F | M | F | M | F | M | F | M | F | M | | | | |
| Sex | | | | | | | | | | | | | | | | |
| Duration of smoking in whole life (as years) | -0.02 | 0.01 | 0.02 | 0.00 | -0.10 | 0.01 | 0.13 | 0.11 | 0.00 | 0.05 | -0.00 | -0.02 | 0.04 | 0.03 | -0.03 | -0.23 |
| Number of cigarettes smoked per day | 0.05 | -0.01 | 0.04 | 0.18 | 0.07 | -0.04 | 0.27* | -0.09 | 0.11 | -0.01 | 0.09 | -0.07 | 0.17 | -0.21 | -0.06 | -0.00 |
| Cigarette use by gestational period ^a | 0.20 | 0.16 | 0.01 | 0.23 | 0.17 | 0.17 | 0.05 | 0.17 | 0.21 | 0.15 | 0.12 | 0.2 | 0.19 | 0.17 | -0.07 | 0.00 |
| Duration of smoking in pregnancy period (as months) | -0.15 | -0.19 | -0.05 | -0.22 | -0.19 | -0.19 | 0.01 | -0.15 | -0.16 | -0.17 | -0.05 | -0.19 | -0.14 | -0.18 | 0.06 | -0.01 |

Spearman Correlation test, r values

*p:0.03

^acategorised <8 weeks, 8-14 weeks, >14 weeks or anytime)



RESULTS:

Prenatal smoke exposure was associated with significantly increased weight-adjusted AGD in female infants at birth (p= 0.03). There was also a significant correlation between mothers' daily smoking rates and weight-adjusted AGD (r= 0.27 / p= 0.03). Fetal smoke-exposure was not associated with any AGD measurements, SPL and penile girth in boys.

CONCLUSION:

A significant increase in weight-adjusted AGD in female infants exposed to maternal smoking may be an indicator of antenatal androgen exposure and may pose a risk for short and long-term endocrine, metabolic and behavioral problems.

In this context, more extensive studies are needed to explain the relationship between maternal smoking and AGD change.

References:

- 1- Fowler PA, Bhattacharya S, Flannigan S, Drake AJ, O'Shaughnessy PJ. Maternal cigarette smoking and effects on androgen action in male offspring: unexpected effects on second-trimester anogenital distance. J Clin Endocrinol Metab. 2011 Sep;96(9):E1502-6.
- 2- Fowler PA, Filis P, Bhattacharya S, le Bizet B, Antignac JP, Morvan ML, Drake AJ, Soffientini U, O'Shaughnessy PJ. Human anogenital distance: an update on fetal smoke-exposure and integration of the perinatal literature on sex differences. Hum Reprod. 2016 Feb;31(2):463-72.
- 3- Smith LM, Cloak CC, Poland RE, Torday J, Ross MG. Prenatal nicotine increases testosterone levels in the fetus and female offspring. Nicotine Tob Res. 2003 Jun;5(3):369-74.
- 4- Håkonsen LB, Ernst A, Ramlau-Hansen CH. Maternal cigarette smoking during pregnancy and reproductive health in children: a review of epidemiological studies. Asian J Androl. 2014 Jan-Feb;16(1):39-49.
- 5- Kandel DB, Udry JR. Prenatal effects of maternal smoking on daughters' smoking: nicotine or testosterone exposure? Am J Public Health. 1999 Sep;89(9):1377-83.