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ORIGINAL PAPER

Prenatal Exposure to Progesterone Affects Sexual Orientation in Humans

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Abstract Prenatal sex hormone levels affect physical and behavioral sexual differentiation in animals and humans. Although prenatal hormones are theorized to influence sexual orientation in humans, evidence is sparse. Sexual orientation variables for 34 prenatally progesterone-exposed subjects (17 males and 17 females) were compared to matched controls (M age = 23.2 years). A case–control double-blind design was used drawing on existing data from the US/Denmark Prenatal Development Project. Index cases were exposed to lutocyclin (bioidentical progesterone = $C_{21}H_{30}O_2$; M_W: 314.46) and no other hormonal preparation. Controls were matched on 14 physical, medical, and socioeconomic variables. A structured interview conducted by a psychologist and self-administered questionnaires were used to collect data on sexual orientation, self-identification, attraction to the same and other sex, and history of sexual behavior with each sex. Compared to the unexposed, fewer exposed males and females identified as heterosexual and more of them reported histories of same-sex sexual behavior, attraction to the same or both sexes, and scored higher on attraction to males. Measures of heterosexual behavior and scores on attraction to females did not differ significantly by exposure. We conclude that, regardless of sex, exposure appeared to be associated with higher rates of bisexuality. Prenatal progesterone may be an underappreciated epigenetic factor in human sexual and psychosexual development and, in light of the current prevalence of progesterone treatment during pregnancy for a variety of pregnancy complications, warrants further investigation. These data on the effects of prenatal exposure to exogenous progesterone also suggest a potential role for natural early perturbations in progesterone levels in the development of sexual orientation.

Keywords Sexual orientation · Prenatal progesterone exposure · Bisexuality · Sexual behavior

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Introduction

Although prenatal gonadal hormones have been theorized to influence sexual orientation in humans, other than recent research using a surrogate measure (2D:4D digit ratio) for prenatal androgen exposure (Hiraichi, Sasaki, Shikishima, & Ando, 2012; Wong & Hines, 2015), evidence from studies of exogenous hormone exposure is sparse (Adkins-Regan, 1988; Ellis & Ames, 1987; Gooren, 2006; Hines, 2011; Hines, Constantinescu, & Spencer, 2015; Meyer-Bahlburg, 1984). Despite relatively frequent current administration of exogenous progesterone to pregnant women with a variety of clinical problems, even less attention has been paid to the possible role of prenatal exposure to progesterone on any aspect of human sexual and psychosexual development (Kester, Green, Finch, & Williams, 1980; Reinisch, Ziemba-Davis, & Sanders, 1991; Sanders & Reinisch, 1985; Wagner, 2008). Perhaps this is due to the elevated levels of natural progesterone present during gestation leading to the assumption that additional exogenous doses would not affect these aspects of development.

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The prenatal hormone or neuroandrogenic theory of sexual orientation (Ellis & Ames, 1987; Gooren, 2006; Hines, 2010; Meyer-Bahlburg, 1984) assumes that heterosexuality is an inherent part of "normal" sexual differentiation and that homosexuality (as evidenced by self-identification, same-sex sexual behavior, or attraction/desire) is a result of perturbations in the typical prenatal hormone environment. Specifically, the theory suggests that homosexuality is the result of insufficient prenatal androgen exposure or action in males and excess prenatal androgen exposure in females during sensitive periods of early development. Thus, homosexuality is viewed as some degree of feminization and/or demasculinization of males and of masculinization and/or defeminization of females. Bisexuality in humans is often thought of as "partial homosexuality" or as moving away from "exclusive heterosexuality" toward a middle point along a bipolar unidimensional continuum between exclusive heterosexuality and exclusive homosexuality (Kinsey, Pomeroy, & Martin, 1948). This bipolar Kinsey scale model implies a trade--off between heterosexuality and homosexuality—the more homosexual, the less heterosexual (see Sanders, Reinisch, & McWhirter, 1990).

For ethical reasons, support for the formative role of prenatal sex hormones in the development of sexual orientation is based primarily on experiments with animals (Adkins-Regan, 1988; Balthazart, 2011; Hines, 2011; Meyer-Bahlburg, 1984), a few clinical studies of humans whose prenatal hormone environments were altered by metabolic anomalies (Cohen-Bendahan, van de Beek, & Berenbaum, 2005; Hines, 2004, 2010, 2011; Jordan-Young, 2012; Meyer-Bahlburg, 1984), or maternal medical treatment with estrogenic compounds during gestation (Meyer-Bahlburg et al., 1995), and most recently the studies using digit ratio measures to reflect the prenatal gonadal hormone environment (Grimbos, Dawood, Burris, Zucker, & Puts, 2010; Wong & Hines, 2015). Critiques (Adkins-Regan, 1988; Balthazart, 2011; Hines, 2011; Meyer-Bahlburg, 1984; Valla & Ceci, 2011) of this perspective and its putative supportive animal research include: (1) conflation of heterotypic sexual behavior in animals (i.e., accepting mounts in males or mounting by females) and human homosexuality (e.g., the male rat who mounts another male is not considered "homosexual," while the mounted male is); (2) limitations in extrapolating from phylogenetically distant animals to humans; and (3) the focus on copulatory (consummatory) behaviors in animal models rather than mate preference (appetitive) behaviors. Additionally, studies in humans are generally limited or complicated by small sample size; inadequate or inappropriate matches or "control" groups; insufficient assessment of sexual orientation or hormone exposure; mixed hormonal exposures; exogenous exposure to synthetic rather than naturally occurring hormones; alterations of genital anatomy related to hormone exposure; confounds with other metabolic and physical correlates of intersex conditions; and/or simultaneous exposures to other treatment compounds. Nonetheless, there is substantial evidence that early exposure to sex hormones influences anatomical, physiological, and sexually dimorphic behavioral development in animals and humans (Cohen-Bendahan et al., 2005; Reinisch, 1974; Reinisch & Sanders, 1984, 1987; Reinisch et al., 1991). Thus, investigation of the role of prenatal sex hormones in the development of human sexual orientation incorporating more effective controls is warranted.

It has been suggested that the potential role of progesterone in mammalian sexual differentiation and development has been insufficiently investigated (Dodd, Jones, Flenady, Cincotta, & Crowther, 2013; Wagner, 2008). Although androgenic, estrogenic, and antiandrogenic compounds have received attention (including synthetic progestins, some of which have androgenic effects), there has been relatively little examination of the role of progesterone, despite its demonstrated antiandrogenic and antiestrogenic effects on some systems (Dorfman, 1967; Sanders & Reinisch, 1985). Progesterone and synthetic progestins are commonly prescribed during early pregnancy for luteal phase support during in vitro fertilization and for threatened abortion (Aboulghar, 2009; Baker et al., 2014, Palagiano et al., 2004) and later in pregnancy for prevention of premature birth and low birth weight (da Fonseca, Bittar, Damião, & Zugaib, 2009).

Few studies have examined the long-term physical and behavioral outcomes of either naturally occurring or synthetic progestin exposure in humans (Cohen-Bendahan et al., 2005; Hartwig et al., 2014; Hines, 2004, 2010; Northen et al., 2007; Reinisch, 1974, Reinisch & Sanders, 1984, 1987; Reinisch et al., 1991). Maternal intake of synthetic progestins and/or progesterone during pregnancy has been found to be associated with increased hypospadias (urinary opening on the underside of the penis instead of the tip) risk in males (Carmichael et al., 2005; Dorfman, 1967; Silver, Rodriguez, Chang, & Gearhart, 1999) and alteration of some sex-differentiated behavior patterns in male and female offspring (Cohen-Bendahan et al., 2005; Ehrhardt, Grisanti, & Meyer-Bahlburg, 1977; Kester et al., 1980; Reinisch, 1974, 1977, 1981; Reinisch & Karow, 1977; Reinisch & Sanders, 1984, 1987; Reinisch et al., 1991; Sanders & Reinisch, 1985).

One of these studies examined the effects of "natural" progesterone on sex/gender development (Kester et al., 1980). It included 10 men (19–24 years) exposed prenatally to natural progesterone alone and a control group matched on date of birth, age of mother, and, in most cases, prior numbers of siblings. Progesterone-exposed subjects "tended to recall boyhood behaviors which departed from the conventional male mode toward 'femininity'" and those subjects exposed to higher doses scored lower on the Bem Sex-Role Inventory Masculine scale and lower on the Feminine scale. A more recent study of fetal exposure to prescription drugs and sexual orientation did not find a significant relationship between maternal reports of progesterone/progestin exposure and sexual orientation, but the study was limited by its

reliance on maternal recall of medical treatment often decades earlier, among other methodological issues (Ellis & Hellberg, 2005).

In light of these findings and the dearth of data on the offspring of progesterone-treated pregnancies, we compared data on sexual orientation and attraction from young adults who were exposed in utero to progesterone (bioidentical progesterone = $C_{21}H_{30}O_2$; M_W: 314.46) via maternal medical treatment to data from unexposed matched controls. The study employed a case–control, double-blind, prospective, longitudinal design using members of a birth cohort with matching of cases and controls on 14 physical, medical, and socioeconomic variables that were recorded prenatally or at birth; careful evaluation of prenatal hormone exposure; and assessment of sexual orientation and attraction. Based upon the limited animal models and human research, we hypothesized that progesterone-exposed human offspring would show more same-sex attraction and behavior with more exposed subjects identifying as non-heterosexual.

Method

Participants

Data from 34 subjects (17 men and 17 women) prenatally exposed exclusively to lutocyclin and no other hormonal preparation, and their individually matched unexposed controls were drawn from an existing database, the US/Denmark Prenatal Development Project (PDP) (Reinisch, Mortensen, & Sanders, 1993). Lutocyclin is identified as progesterone (bioidentical progesterone = $C_{21}H_{30}O_2$; M_W: 314.46) in the Danish Physician's Desk Reference (Junager & Schleisner, 1963) and was administered during pregnancy to treat cases of potential miscarriage as indicated by staining or bleeding, abortion imminens (threatened abortion), or maternal history of repeated miscarriage. Mean age of the participants at the time of assessment for this study was 23.2 years (SD = 1.4).

Participants were drawn from the Copenhagen Perinatal Cohort, comprising all 9125 offspring born at the University Hospital in Copenhagen, Denmark, between 1959 and 1961. During the establishment of the cohort, demographic, socioeconomic, and medical variables were prospectively recorded pre-, peri-, and postnatally. Potential participants for the current study were identified through the available computerized database. Exclusion criteria were: offspring of incest; gestation length less than 28 weeks; congenital malformation (including genital ambiguity); Down's syndrome; maternal history of diabetes, epilepsy or CNS disorder; maternal treatment with thyroid medication; maternal psychosis or syphilis; mother less than age 16 at time of delivery; and mother diagnosed with polio, encephalitis, meningitis, viral pneumonia, or ornithosis during pregnancy. The original datatape only coded yes/no for drug exposure in terms of the class of drug administered (hormone, barbiturate, antiepileptic, etc.) for at least 5 days during each of six gestational periods, coded into trimesters for these analyses. Original hospital records for all hormone-exposed cases and their matched controls were reviewed by our team to confirm exclusion criteria and to obtain specific information on dosage, timing, and duration of exposure to all gestational treatments. All eligible cases were recruited to participate in the PDP. The overall participation rate for the PDP was 87%. Extensive details of the methodology are reported elsewhere (Reinisch et al., 1993; Reinisch, Sanders, Mortensen, & Rubin, 1995). Participants only knew they were recruited due to their inclusion in the Danish Perinatal Cohort at birth but were blind as to their exposure status.

Of the 45 cases exposed to lutocyclin in the PDP database, the 34 included here were those exposed to lutocyclin and no other hormonal preparation, so that any observed effects of lutocyclin would not be confounded by exposures to other hormones. Matches were chosen from 271 non-exposed controls selected from a large pool of similarly evaluated PDP members.

Matching occurred in two stages using 14 variables with exact matching for sex. The objective of the matching was to obtain a set of control subjects whose distributions on matching variables were as close as possible to the distributions of exposed subjects. First, using Mahalanobis metric matching within calipers defined by the estimated propensity score for each exposed case, the 10 statistically best potential controls were identified (Rosenbaum & Rubin, 1985a, 1985b) and then the Project Director (J.M.R.) matched one or two potential controls to each exposed case for inclusion in the study. Details of the matching procedure have been published elsewhere (Reinisch et al., 1993, 1995). Table 1 shows that there were no significant group differences (exposed vs. unexposed) in the distributions of matching variables.

When the Perinatal Cohort was established, pregnant women were interviewed as soon as they were enrolled for prenatal care about whether they were married or single, had planned the pregnancy at the time of conception, or had attempted abortion (Villumsen, 1970). For exposed cases, there was one single mother (2.9%), one unplanned pregnancy (2.9%, not the same person), and no abortion attempts. For the matched control sample, 23% of the mothers were single, 44% of the pregnancies were unplanned, and 12% had attempted abortion. The percentages for the overall cohort were 37, 56, and 7%, respectively. It is not surprising that special treatment for pregnancy maintenance was confounded with being married, planning or wanting the pregnancy, and not attempting abortion. Therefore, these were not used as matching variables. At the time, relatively few couples were living together without being married and being a single mother may have presented difficulties. We do not interpret these potential confounds as potential causative factors for same-sex (homosexual/bisexual) behavior and attraction. In the PDP sample of more than 550 participants, these three mater-

Table 1 Distributions of matching variables for prenatally progesterone-exposed and unexposed participants

Matching variable	Exposed $n = 34$	Unexposed $n = 34$	Statistic[a]	p
% Male[b]	50.0	50.0	na	
% Firstborn	61.8	50.0	$z = .85$	ns
Mean (SD) gestation length (week)	37.76 (3.10)	38.12 (1.80)	$t(32) < 1$	ns
Mean (SD) birth weight (g)	31.13 (8.85)	30.99 (5.06)	$t(33) < 1$	ns
Mean (SD) birth length (cm)	50.97 (4.66)	50.69 (2.29)	$t(33) < 1$	ns
Mean (SD) socioeconomic status[c]	6.00 (1.55)	5.94 (1.52)	$t(31) < 1$	ns
Mean (SD) breadwinner's education[d]	3.07 (.78)	3.06 (.74)	$t(29) < 1$	ns
Mean (SD) mother's age (year)	30.03 (4.46)	31.15 (5.76)	$t(33) = -1.06$	ns
Mean (SD) father's age (year)	35.00 (6.03)	33.48 (7.12)	$t(32) = 1.04$	ns
Mean (SD) PBC 415[e]	33.85 (17.91)	33.53 (16.12)	$t(33) < 1$	ns
Mean (SD) maternal complaint score[f]	2.96 (2.48)	3.22 (2.52)	$t(33) < 1$	ns
% Severe preeclampsia	3.0	2.9	$z = 0$	ns
% Maternal respiratory illness	2.9	2.9	$z = 0$	ns
Mean (SD) maternal weight gain (kg)/height cubed (m) Wgt/hght	25.52 (9.05)	25.29 (7.35)	$t(23) < 1$	ns
Mean (SD) no. of cigarettes/day in third trimester	4.42 (7.01)	5.74 (7.64)	$t(32) < 1$	ns

[a] na = Not applicable. Unless otherwise noted $df = 33$

[b] Exact match required for sex

[c] Family socioeconomic status when the child was 1 year of age. Danish system categorized on an eight-point scale, 1 = lowest, 8 = highest. Pairs were exactly matched on SES, except for two exposed cases with missing data who were matched to controls with SES = 4

[d] Education was categorized on a four-point scale, 1 = remedial instruction, 4 = college

[e] The predisposing risk score is a variable in the original cohort datatape. It is a score based on pregravidas factors concerned with the mother's physical and emotional state prior to the pregnancy. Information includes such items as whether the mother was married when she conceived, whether she had previously had an abortion, a miscarriage, a stillbirth, or neonatal death; her age; her weight; and previous history of central nervous system illness, syphilis, cardiovascular illness, or diabetes. The score indicates that conditions (physical and emotional) were probably "less than optimum" for conception at the time. For the cohort, the scores range from 0 to 130 and the mean is 29.52

[f] The maternal complaint score included the following: severe preeclampsia, hypertension, prescription of diuretics, edema and proteinuria, bleeding/staining, allergies and treatment with antihistamines, and anemia

nal variables were unrelated to offspring sexual orientation, attraction, or sexual behavior in either sex.

Lutocyclin exposure parameters in the present sample were as follows: Mean total dosage was 915 mg (SD = 1073.54, range 40–5400 mg) with a mean treatment duration of 61 days (SD = 42, range 8–158). Average daily dose was calculated for each individual by dividing total dosage by duration of treatment. The group mean of "average daily dose" was 18.41 mg/day. Forty-one percent ($n = 14$) were exposed during the first trimester only, 35% ($n = 12$) during the first and second trimesters, 17% ($n = 6$) during the second trimester only, and 6% ($n = 2$) during the second and third trimesters. Table 2 shows detailed information on dosage and timing of exposure. No minimum exposure parameters were set for selection; thus, these represent the normal range of dosages and durations commonly used in treatment of at-risk pregnancy in Denmark during this period. Exposures did not differ by sex. Timing of exposure occurred during periods associated with sexual differentiation of the CNS in humans.

Measures

Interview Data

Information on sexual orientation was obtained as part of a structured interview conducted by a psychologist at the Institute for Preventive Medicine in Copenhagen, Denmark. Psychologists were blind to the exposure status of all subjects. The following sexual orientation variables were addressed in the comprehensive interview and coded as follows.

Same-Sex Variables

1. Self-labeled sexual orientation: (heterosexual/non-heterosexual) [This item was drawn from a question asking participants whether they considered themselves to be heterosexual, homosexual, bisexual, "don't know." Given the small numbers in the non-heterosexual categories, the data were recoded to heterosexual/non-heterosexual for analysis.]

Table 2 Descriptive statistics for progesterone exposure variables ($n = 34$)

Progesterone exposure variables	*N*	(%)
Timing of exposure (trimesters)		
1st only	14	41.2
1st–2nd	12	35.3
2nd only	6	17.6
2nd–3rd	2	5.9
3rd only	0	0.0
Total dosage (mg)		
40–300	11	32.4
301–999	14	41.2
1000–1999	5	14.7
2000–5400	4	11.8
Duration of exposure (days)		
8–29	9	26.5
30–60	12	35.3
61–120	8	23.5
121–158	5	14.7
Average daily dosage (mg/day)		
3–9	16	47.1
10–25	7	20.6
26–50	11	32.4

2. Lifetime attraction to own sex: (yes/no)
3. Current attraction to own or both sexes: (yes/no)
4. Kissed own sex: (yes/no)
5. Having been partially undressed in a sexual situation with own sex: (yes/no)
6. Having been fully undressed in a sexual situation with own sex: (yes/no)
7. "Intercourse" with own sex: (yes/no) [Our interview data indicated that women generally interpreted this question to mean mutual genital sexual stimulation; men usually interpreted this as anal intercourse.]

Other-Sex Variables

8. Having kissed other ("opposite") sex: (yes/no and age at first engagement)
9. Having been partially undressed in a sexual situation with other sex: (yes/no and age at first engagement)
10. Having been fully undressed in a sexual situation with other sex: (yes/no and age at first engagement)
11. Intercourse with other sex: (yes/no, and age at first engagement).

Items 4–11 were coded from questions asking age at first participation in each behavior, an approach developed by Kinsey (Kinsey et al., 1948; Kinsey, Pomeroy, Martin, & Gebhard, 1953). Asking age at first engagement signals participants that one is non-judgmental about their engagement in particular sexual behaviors. A postpubertal criterion was applied for age at first engagement in these behaviors. Specifically, age at puberty (which was assessed by a separate set of questions about markers of puberty) was compared to the reported age at first engagement in the behaviors. The very few reports of behaviors prior to puberty were not included in these analyses as they could have been childhood sexual exploration. This criterion was consistently applied across all subjects and for both same-sex and other-sex behaviors. The number of participants engaged in the same-sex behaviors was insufficient to conduct a statistical analysis of age for those variables. However, we were able to analyze age at first engagement in the heterosexual behaviors.

Questionnaire Data

Sexual Behavior Inventory (SBI) This self-administered questionnaire was created for the PDP (Reinisch et al., 1993) to assess whether or not 67 different sexual behaviors have been tried. Three items on the questionnaire were relevant to sexual orientation: (1) to "go to bed with" a person of your own sex (in Danish, this item is understood to mean intercourse or mutual genital contact); (2) to masturbate in the presence of another person(s) of the same sex; and (3) to masturbate in the presence of another person(s) of the opposite sex.

Sexual Attitudes Questionnaire (SAQ) This self-administered questionnaire, created for the PDP (Reinisch et al., 1993), includes 120 items from the original Eysenck Inventory of Attitudes toward Sex (Eysenck, 1976). Participants indicated their agreement/disagreement on a three-point scale (yes, ?, no; scored 2, 1, 0, respectively) with 179 statements about various aspects of sexuality. There are two factors relevant to sexual orientation: attraction to males and attraction to females. Each factor has six items and shows good internal consistency (Cronbach's alphas .88 for attraction to males and .90 for attraction to females). Items for attraction to males and attraction to females were worded identically except for the sex of the object of attraction. Questions (in Danish) were scattered throughout the SAQ. The 12 questions about attraction to males/females translated into English are as follows:

- I usually take a long look when I meet an attractive man/woman in the street.
- Male/female sexual organs are attractive.
- I often have fantasies about male/female sex partners.
- Now and then I think about sex when I am in an attractive man's/woman's company.
- I sometimes have fantasies about being with two or more men/women at the same time.
- I regularly meet men/women whom I find attractive.

Procedure

The study was approved by the appropriate review boards for the protection of human subjects in both the U.S. and Denmark. The data presented in this article assessing sexual orientation represent a subset of a large evaluation battery (Reinisch et al., 1993). The purpose and procedures for the study were explained to participants, and informed consent was obtained. A psychologist supervised the collection of questionnaire data and conducted the interview during a full day of evaluation at the Institute for Preventive Medicine. Evaluators and participants were blind regarding treatment status.

Data Analysis

We hypothesized that same-sex behavior and attraction would be higher for the exposed compared to the unexposed participants. Data were first examined for interactions between sex of participant and exposure to lutocyclin. Finding none, data from men and women were then combined for statistical analysis of exposure effects, with the exception of scores for attraction to males and attraction to females as these are more easily understood when presented separately by sex. For dichotomous variables, Tango's (1998) test of the differences in proportions in matched pairs was used. Unlike the McNemar test, Tango's test accommodates 2×2 tables with off-diagonal zero cells. For continuous variables, paired t tests were performed to compare data from exposed and unexposed participants. Spearman's rho was used to evaluate the correlation between attraction to males and attraction to females. Relationships between progesterone treatment parameters and outcomes of interest were assessed by the Kolmogorov–Smirnov Z test of equality of distributions. We report p values for two-tailed tests, a conservative criterion given our directional hypotheses which would justify use of one-tailed tests.

Results

As shown in Table 3, compared to their matched controls, exposed cases showed a consistent pattern of higher percentages of:

1. Self-labeled identification as other than heterosexual (i.e., homosexual, bisexual, or "don't know") (20.6% exposed, 0% controls, $p < .01$). Among the exposed men, one identified as homosexual, two as bisexual, and two said "don't know." Among exposed women, two identified as bisexual. All other subjects, exposed and unexposed, self-identified as heterosexual;
2. "Ever Attracted to Own Sex" (29.4% exposed, 5.9% controls, $p = .02$);
3. "Currently Attracted to Own or Both Sexes" (17.6% exposed, 2.9% controls, $p < .06$); and
4. Various sexual behaviors with their own sex including "kissed own sex"; partially and fully undressed in a sexual situation; "intercourse"; "gone to bed"; and "masturbated together" (range 14.7–24.2% exposed cases, 0–9.1% of controls). In general, behavioral patterns were consistent for individuals. For example, all those reporting "intercourse" with a person of the same sex also reported "going to bed" with; being fully and partly undressed in a sexual situation with; and kissing someone of the same sex.

None of those who identified as other than heterosexual had own sex attractions or engaged in these same-sex behaviors were concordant with their matches.

Exposure status was not associated with heterosexual experience—all participants reported sexual behavior with the other sex. The small number of cases who engaged in same-sex sexual behaviors precluded statistical analyses of "Age at First Engagement" in those behaviors, but this measure for heterosexual behaviors did not differ according to exposure status (see Table 4).

For men, scores on the attraction to males scale were significantly higher for exposed cases compared to controls, paired $t(16) = 2.76$, $p < .02$, two-tailed, but scores did not differ for the attraction to females scale (see Table 5). For women, scores on attraction to females scale were not different between exposed and unexposed cases, but there was a statistical trend toward higher scores on the attraction to males scale for exposed women, paired $t(16) = 1.92$, $p = .07$, two-tailed. Thus, exposure was positively associated with higher scores on the attraction to males scale regardless of sex, total group of males, and females combined paired $t(33) = 3.31$, $p < .01$, two-tailed. Although a bipolar model of sexual orientation (Kinsey et al., 1948; Sanders et al., 1990) would predict a strong negative relationship between scale scores for attraction to males and attraction to females, this was not the case (for men, Spearman's rho $= -.10$; for women, rho $= .23$; both ns).

In light of findings linking birth order and number of older brothers to homosexual orientation among men (Blanchard & Bogaert, 1996; Cantor, Blanchard, Paterson, & Bogaert, 2002), this possible confound was examined. Neither birth order nor a number of older brothers confound the current findings. Not surprising given the matching, birth order did not differ between exposed and unexposed men ($M = 1.76$, SD $= .96$) and the number who had older brothers was the same for the exposed and unexposed groups ($n = 5$ for each group).

A systematic investigation of the relationship between progesterone treatment parameters (i.e., total dosage, average daily dosage, timing, and duration of progesterone exposure) and outcomes of interest was precluded by the high variability in maternal medical treatment and the intercorrelations among the various treatment parameters. Nonetheless, it is noteworthy that the seven individuals who self-identified as other than heterosexual

Table 3 Comparison of sexual orientation, attraction, and behavior variables for prenatally progesterone-exposed (Exp) and unexposed (Un) participants

	Men (17 pairs)		Women (17 pairs)		Total group (34 pairs)				z Statistic[a]	p (two-tailed)[b]
	Exp	Un	Exp	Un	Exp		Un			
	n	n	n	n	n	(%)	n	(%)		
Same sex										
Non-heterosexual self-labeled identity[c,d,e]	5	0	2	0	7	20.6	0	0	2.56	.008
Ever attracted to own sex[c]	6	0	4	2	10	29.4	2	5.9	2.31	.021
Current attraction to own or both sexes[c,e]	3	0	3	1	6	17.6	1	2.9	1.88	.059[b]
Kissed own sex[c,e]	3	0	4	1	7	20.6	1	2.9	2.12	.034
Has been partially undressed in a sexual situation with own sex[c,e,f]	3	0	4	1	7	20.6	1	2.9	2.12	.034
Has been fully undressed in a sexual situation with own sex[c,e,f]	2	0	4	1	6	17.6	1	2.9	1.88	.059[b]
"Intercourse" with own sex[c,e,f]	2	0	3	0	5	14.7	0	0	2.23	.025
"Gone to bed" with person of own sex[e,f,g]	2	0	4	1	6	17.6	1	2.9	1.89	.059[b]
Masturbated in the presence of same sex[g]	6	2	2	1	8	24.2	3	9.1	1.67	.095[b]
Other ("opposite") sex										
Kissed other sex[c]	17	17	17	17	34	100	34	100	na	na
Has been partially undressed in a sexual situation with other sex[c]	17	17	17	17	34	100	34	100	na	na
Has been fully undressed in a sexual situation with other sex[c]	17	17	17	17	34	100	34	100	na	na
Intercourse with other sex[c,h]	16	17	17	17	33	97.1	34	100	1.00	ns
Masturbated in the presence of other sex[g]	6	8	4	6	10	30.3	14	42.4	1.15	ns

[a] Tango's (1998) test of the differences in proportions in the pair-sample design was used (na = Not applicable)

[b] We have used a conservative criterion for statistical significance. The hypotheses are directional, and therefore, one-tailed tests may be justified. If one-tailed tests are used, all same-sex variables in this table would be significant at $p < .05$ (na = Not applicable)

[c] From the interview

[d] Self-identification as lesbian, homosexual, bisexual, or "don't know" was recoded as non-heterosexual. Specifically, among the exposed men one identified as homosexual, two as bisexual, and two said "don't know." Among exposed women, two identified as bisexual. All other subjects, exposed and unexposed, self-identified as heterosexual

[e] None of those who identified as other than heterosexual; had own sex attractions; or engaged in these same-sex behaviors, were concordant with their matches

[f] In general, behavioral patterns were consistent for individuals. For example, all those reporting "intercourse" with a person of the same sex, also reported "going to bed" with, being fully and partly undressed in a sexual situation with, and kissing someone of the same sex

[g] From the Sexual Behavior Inventory

[h] Only one participant, a lutocyclin-exposed man (who reported same-sex "intercourse"), did not report having had heterosexual intercourse

were exposed to higher total dosages (median = 1000 mg, range 450–5400 mg) over longer durations (median = 105 days, range 20–120 days) than those who identified as heterosexual (median total dosage = 500 mg, range 40–2700 mg, K–S $Z = -2.28$, $p = .02$; median duration = 47 days, range 8–158 days, K–S $Z = -2.24$, $p < .03$).

Discussion

In summary, we observed consistent findings across samples of men and women prenatally exposed to exogenous progesterone for a set of variables directly reflective of sexual orientation. Relative to unexposed controls, prenatal exposure to progesterone was significantly associated with: (1) decreased likelihood of self-identification as heterosexual; (2) increased likelihood of having engaged in same-sex sexual behaviors; (3) increased likelihood of reporting attraction to the same or both sexes, and (4) higher scores on the attraction to males scale. Progesterone exposure was not associated with a decrease in measured heterosexual behavior. Among progesterone-exposed cases, non-heterosexual identity was shown to be associated with higher total dosages and longer duration of prenatal exposure to progesterone.

We recognize that many factors may affect the development of sexual orientation and that the prenatal hormone environment is only one of these. In considering the epigenetic mechanism(s) by which prenatal exposure to exogenous progesterone may influence sexual orientation, it is relevant that progesterone appears to have both antiandrogenic and antiestrogenic potential during early critical or sensitive periods of development (Connolly, Handa, & Resko, 1988; Dorfman, 1967; Kester et al., 1980; Sanders

Table 4 Comparison of ages of first engagement in sexual behaviors with other sex for prenatally progesterone-exposed and unexposed participants (34 pairs)

Other-sex variable	Exposed *M* (SD)	Unexposed *M* (SD)	Paired *t*	*p*
Age at first kissing other sex (years)	13.81 (2.77)	13.10 (.40)	1.21	ns
Age at first being partially undressed in a sexual situation with other sex (years)	14.82 (2.43)	14.10 (2.60)	1.33	ns
Age at first being fully undressed in a sexual situation with other sex (years)	15.72 (2.50)	14.97 (2.43)	1.35	ns
Age at first intercourse with other sex (years)	16.39 (2.29)	15.81 (2.75)	1.02	ns

Table 5 Comparison of scores for attraction to males and attraction to females for prenatally progesterone-exposed (Exp) and unexposed (Un) participants within sex

Score	Males (17 pairs)				Females (17 pairs)			
	Exp	Un	Paired *t*	*p* (two-tailed)	Exp	Un	Paired *t*	*p* (two-tailed)
Attraction to males								
M	.52	.13	2.76	.014	1.57	1.40	1.92	.073
SD	.56	.18			.29	.48		
Attraction to females								
M	1.76	1.81	<1	ns	.75	.58	<1	ns
SD	.43	.23			.54	.51		

Possible scores ranged from 0 to 2

& Reinisch, 1985). Exogenous progesterone has been demonstrated to have physiological effects during gestation despite the presence of high endogenous levels (Aboulghar, 2009; da Fonseca et al., 2009; Palagiano et al., 2004; Silver et al., 1999). Exogenous progesterone administrated in association with in vitro fertilization has been suggested as a factor in increased rates of hypospadias in male newborns (Carmichael et al., 2005; Dorfman, 1967; Silver et al., 1999). Additionally, emerging research with rodents suggests progesterone and progesterone receptors may play an important role in the development of dimorphic sexual, cognitive, social, and affective behavior differentiation (Wagner, 2008; Wagner, Nakayama, & De Vries, 1998). While the direct physiological mediators of the effects of prenatal progesterone exposure await identification, our findings may be considered a behavioral bioassay of such underlying effects (Reinisch, 1974; Reinisch et al., 1991). This bioassay makes it clear that exposure to exogenous progesterone during a sensitive period of human CNS differentiation may permanently affect neural function and ultimately influence later behavior. It is also possible that medical treatment with progesterone is a marker of maternal progesterone deficiency and that variation in endogenous maternal progesterone levels may be an important factor in naturally occurring differences in sexual orientation. The detection of a relationship between prenatal exposure to exogenous progesterone and sexual orientation in early adulthood, despite many intervening factors, supports the hypothesis that the prenatal hormone environment is influential.

How might the addition of exogenous progesterone into an already rich mixture of gestational steroids, including endogenous progesterone, affect the nervous system and subsequent behavioral development of the offspring? First, in keeping with the most current clinical research, this hormonal medication was, and continues to be, administered by physicians to treat symptoms of staining, bleeding, to prevent prematurity in twins (Rouse et al., 2007; Schuit et al., 2015), and to prevent preterm birth (Dodd et al., 2013; Merlob, Stahl, & Klinger, 2012) and for imminent spontaneous abortion (da Fonseca et al., 2009). This demonstrates its capacity to have some meaningful physiological impact. It is currently used for pain, uterine contractions, and inadequate luteal phase, and its effectiveness has been demonstrated on both ultrasound assessment of uterine contraction and a pain scale (Palagiano et al., 2004). Second, progesterone was administered exogenously at pharmacological levels during periods of gestation known to be sensitive to the influence of steroid hormones on sexual development (see Table 2). Third, exogenously introduced hormones may differ from (and thus have different potency than) their endogenous counterparts in how they are metabolized, their receptor affinity and sensitivity, and their systemic versus localized action. Thus, it is possible that, compared to endogenous levels, even relatively limited physiological doses may have significant effects on various systems when administered exogenously.

A limitation common to studies of sexuality is their reliance on self-report. The non-normative status of same-sex attraction and behavior tends to produce a social desirability effect toward underreporting these behaviors. Any such bias would have served to minimize differences between groups. Similarly, small sample size often results in limited statistical power. It is also important to note that in research on human prenatal exposures, our 34 cases with a single unconfounded type of hormonal exposure represent an unusually large number. More detailed evaluations of treatment parameters were not possible given the wide range of individual treatment regimes and the colinearity of the treatment variables. Despite the variation in treatment regimens, the extensive comparable prospective data available on both index cases and controls provide confidence in the treatment status for both groups and a relatively large pool of matching variables. Our groups were carefully matched on 14 highly relevant prenatal, perinatal, and maternal factors which should serve to minimize confounds in comparisons between exposed and control subjects. It should be taken into account that participants were in their early to mid-20s when evaluated and that the lifetime range of their patterns of sexual behavior and attractions was not likely to have been fully realized by early adulthood. Follow-up studies would be required to evaluate the levels of same-sex behavior and/or attraction that may have been revealed in subsequent decades. In keeping with the strengths of the current design, we found consistent statistically significant effects across a number of different measures supporting our hypotheses.

What are the theoretical implications of our findings regarding the conceptualization of the nature of sexual orientation and its biological bases? Support for the commonly held bipolar model of sexual orientation (a unidimensional model where one pole represents homosexuality and the other, heterosexuality or masculinity vs. femininity; Kinsey et al., 1948) requires a strong negative correlation between scale scores on attraction to males and attraction to females (Sanders et al., 1990) as well as that between same and opposite sex experience. However, our study fails to support this model since in both males and females these correlations were low and not significant. Therefore, we hypothesize that sexual orientation may be more accurately and productively conceptualized in terms of a two-dimensional model in which the dimensions of heterosexuality and homosexuality are relatively independent, with each dimension having a high and low pole, perhaps reflecting different neurodevelopmental pathways (Olvera-Hernandez, Chavira, & Fernandez-Guasti, 2015; Sanders et al., 1990; Storms, 1988). Such a perspective fits well with similar models we have described for the differentiation of masculinity and femininity in the context of the development of more general aspects of gender identity and role (Reinisch & Sanders, 1987; Reinisch et al., 1991). Methodologically, our results emphasize that studies of sexual expression, which focus on same-sex or "opposite"-sex behavior to the exclusion of the other, may obscure the prevalence of bisexual patterns.

In conclusion, these findings reveal that prenatal progesterone has been an underappreciated factor in human psychosexual development (as are the actions of fetal testosterone or externally introduced endocrine disruptors). Our findings suggest that natural perturbations in endogenous progesterone during gestation may affect individual differences in the expression of adult sexual orientation. Specifically, progesterone exposure was found to be related to increased non-heterosexual self-identification, attraction to the same or both sexes, and same-sex sexual behavior. The findings challenge the prevailing view of homosexual interest and behavior as a simple reflection of feminization/demasculinization in males and masculinization/defeminization in females. In contrast, the current research underlines the necessity of concurrent measurement of a wide spectrum of both same-sex and "opposite"-sex behaviors and attitudes in any study of human sexual expression.

The current findings highlight the likelihood that prenatal exposure to progesterone may have long-term behavioral sequelae related to sexuality in humans, even in the absence of morphological effects on the genitalia. In light of the continued treatment of human pregnancies with progesterone (and other progestogens), further studies of offspring of progesterone-treated pregnancies are warranted and may provide important insights into the role of this hormone in human behavioral development (Dodd et al., 2013).

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval Existing data from human research participants were used. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent At the time of data collection, informed consent was obtained from all individual participants included in the study.

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