Archives of Sexual Behavior, Vol. 6, No. 4, 1977

Prenatal Exposure to Synthetic Progestins and Estrogens: Effects on Human Development

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Seventy-one offspring of mothers administered combinations of synthetic progestins and estrogen for the maintenance of at-risk pregnancy were evaluated for their performance on IQ and personality tests. Siblings born of untreated pregnancies acted as controls. Hormone-exposed subjects were partitioned into three treatment subgroups dependent on the ratio of progestin to estrogen administered to their mothers during pregnancy. No difference in IQ was obtained among the three treatment subgroups even when scores were adjusted for sibling score and prenatal and perinatal complications. Responses to the personality questionnaire provided significant differences among the three groups. The group exposed to the progestin regime (progestin alone or in combination with very low doses of estrogen) and the estrogen regime (higher doses of estrogen than progestin) were most dissimilar. Progestin regime exposed subjects were characterized as more independent, sensitive, self-assured, individualistic, and self-sufficient. In contrast, the subjects exposed to the estrogen regime were more group oriented and group dependent. Analysis of difference scores generated by subtracting the score of an unexposed sibling from that of the exposed cosibling provided similar results. A general discussion is presented on the efficacy of hormone treatment for pregnancy maintenance, augmented fetal wastage of males, birth order and treatment, maternal knowledge of treatment and its possible postnatal effects on the offspring, and drug effects on the fetus.

KEY WORDS: synthetic progestin; estrogen; diethylstilbestrol; humans; personality; IQ; pregnancy maintenance; prenatal.

Original research was supported by Research Grant No. NE-G-00-3-0106, National Institute of Education, the Ford Foundation, the Erickson Educational Foundation, and Behavioral science Research Grant, U.S. Public Health Service to J. Reinisch.

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INTRODUCTION

Data related to the hypothesis that steroid hormones affect neural (CNS) tissue during development and thereby influence intelligence and personality come primarily from experimental animal research and human clinical studies. It has been demonstrated that the presence, during critical periods in development, of exogenously introduced or endogenously produced steroids, especially androgens, affects both reproduction-linked (mating) behavior and dimorphically expressed nonmating behavior such as aggression, play, wheel running, and open-field activity. This has been shown in rats, guinea pigs, mice, hamsters, and rhesus monkeys. Masculinization or defeminization of genital morphology results from exposure to androgens, while their absence results in feminization or demasculinization. Furthermore, studies spanning the last 35 years have demonstrated that CNS tissue is modified functionally, anatomically, histologically, and in metabolic activity by the presence or absence of androgen during critical periods of early development. Many of these effects which occur normally under the influence of androgen can be mimicked by administration of estrogen (see Reinisch, 1974, 1976, for more detailed discussion).

In humans, studies of syndromes with endocrine involvement such as adrenogenital (Ehrhardt *et al.*, 1968a,b; Ehrhardt and Baker, 1974; Money *et al.*, 1967; Money and Lewis, 1966; Money and Meredith, 1967), androgen insensitivity (Masica *et al.*, 1969; Money *et al.*, 1968), and Turner's (Ehrhardt *et al.*, 1970; Money and Ehrhardt, 1968; Money *et al.*, 1967) have indicated that gender-related behavior and genital morphology are affected by the amount of steroid hormones present during critical periods in prenatal development.

Treatment with progestins during critical periods has been reported to have androgenic effects on female animals (Greene *et al.*, 1939; Lerner *et al.*, 1962; Piotrowski, 1968a,b; Revesz *et al.*, 1960; Schöler and de Wachter, 1961; Suchowsky and Junkmann, 1961; Whalen *et al.*, 1966). Progesterone (Grumbach and Ducharme, 1960; Hayles and Nolan, 1958; Jones and Wilkins, 1960; Reilly *et al.*, 1958; Wilkins *et al.*, 1958), synthetic progestins (Burstein and Wasserman, 1964; Fine *et al.*, 1963; Grumbach *et al.*, 1959; Hagler *et al.*, 1963; Hayles and Nolan, 1957; Jacobson, 1961; Wilkins, 1960; Wilkins *et al.*, 1958), and estrogenic hormones (Bongiovanni *et al.*, 1959; Grumbach and Ducharme, 1960; Grumbach *et al.*, 1959; Jones and Wilkins, 1960; Wilkins, 1960; Wilkins *et al.*, 1958) have also been implicated in a small percentage of cases in which human females were born with masculinized genitalia after their mothers were treated with these hormones for spontaneous abortion or toxemia of pregnancy.

Paradoxically, Courrier and Jost (1942) and Diamond *et al.* (1973) have reported a feminizing (demasculinizing) effect on males of synthetic progestins in rabbits and progesterone in rats when exposure occurred during early periods of development. Aarskog (1970) presented five cases of hypospadias (incomplete

masculinization) in human males whose mothers had been treated with synthetic progestin during pregnancy, demonstrating a similar feminizing effect.

Maternal treatment with estrogens (including diethylstilbestrol, DES, a synthetic nonsteroidal estrogen) for the maintenance of pregnancy has been implicated in a number of cases in which female fetuses were born with masculinized genitalia (Bongiovanni *et al.*, 1959). In other reports DES and conjugated equine estrogen (Premarin) (Grumbach and Ducharme, 1960; Grumbach *et al.*, 1959; Jones and Wilkins, 1960; Wilkins, 1960; Wilkins *et al.*, 1958) were administered in addition to progestins. Although the estrogen could not be credited with being the active agent, "these substances certainly did not prevent fetal masculinization" (Wilkins, 1960). As Walker and Money (1972) noted in a review of a number of these cases: "The affected children born to these mothers were as likely to be masculinized as were those children born to non-estrogen-treated mothers who took progestins." Hypospadias in males who were exposed to DES *in utero* has been reported by Kaplan (1959) and Yalom *et al.* (1973). It would seem that the paradoxical effects of masculinization (defeminization) of females and feminization (demasculinization) of males found as a result of exposure to progestins in humans and animals are characteristic of treatment with estrogen as well.

PRENATAL HORMONE EXPOSURE IN HUMANS

There are studies with humans subjects which are directly related to the present inquiry. Three are concerned with the influence of prenatal exposure to progestational hormones on IQ and personality variables and the fourth investigated the effects of DES.

Progestins

Ehrhardt and Money (1967) published a study of ten girls treated prenatally with synthetic progestins in which detailed inquiry was made into IQ and personality development. Analysis of extensive interviews given to both the subjects and their mothers demonstrated an unusually high degree of "tomboyism" in these treated subjects. Tomboyism was defined as "play with boys' toys; athletic energy; outdoor pursuits; and minimal concern for feminine frills, doll play, baby care, and household chores." Unexpectedly, the subjects also evidenced extraordinarily high IQs as measured by the Wechsler Intelligence Scale for Children. The mean IQ of the group was 125, with a standard deviation of 11.8. Sixty percent of the IQs were above 130, when only 2% would be predicted from a random sampling of the normal population. Although Ehrhardt and Money tentatively concluded that the findings could be viewed as preliminary evidence

of the effects of prenatal treatment with progestins on the central nervous system, because of the small sample size, the concomitant possibility of sampling bias, and the absence of a matched control group they cautioned against unrestrained interpretation of their data.

In 1968, Dalton published data which lent added credence to the findings of Ehrhardt and Money. Dalton studied achievement ratings made by teachers of 29 British 9- and 10-year-old children prenatally exposed to progesterone. The mothers of these children were administered progesterone for toxemia of pregnancy. The next child born in the labor ward of a normal pregnancy and delivery served as a normal control and the next child born of an untreated toxemic mother as a toxemic control. An analysis of the data revealed that the prenatally progesterone-exposed subjects received significantly more "above average" grades than did either of the control groups in academic subjects including verbal reasoning, English, and arithmetic. Although caution was suggested in interpreting these results because of the possibility of selection bias, Dalton did find the effects to be dosage dependent – those subjects whose mothers had received over 8 g of progesterone received significantly better ratings than those getting less than 8 g. Results were also related to time of onset of treatment in pregnancy: "a significant improvement in educational performance was demonstrated among children who received progesterone before the 16th week."

A follow-up on the British sample was presented at the Society for Research in Child Development which seemed to confirm Dalton's (1968) earlier findings while providing additional information on personality development in progesterone-treated children (Zussman *et al.*, 1975). However, there are serious problems with the report, most importantly regarding the sample selection and description. The new sample included some of the treated and control children from the 1968 investigation (now 10 years older) and new progesterone-exposed subjects from a general medical practice with controls matched "for sex, birthweight, SES, blood group, mother's age, and family size . . . ." The authors began with a population of 65 progesterone-treated children and 96 children in the control group ranging in age from 16 to 19 years. The majority of the families were identified as working class. However, "the final sample of subjects interviewed included only 30 progesterone children (12 females, 18 males) and 29 controls (12 females, 17 males)." Information was not given on the age range of the final sample, on whether the matching held up even though attrition was so high, and on how many of the subjects from the 1968 sample were a part of the new group.

Results from the Differential Aptitude Test suggested that hormone-exposed children showed a clear advantage in Numerical Ability. This advantage was significantly related to higher dosage and a duration of treatment longer than 8 weeks. Scores on the BEM Sex-Role Inventory and the California Psychological Inventory demonstrated no relationship between prenatal progesterone treatment

and masculinity-femininity for either sex. Responses to a retrospective interview on behavior from 5 to 10 years of age revealed the following significant results: Females exposed to progesterone reported less tomboyish interests and behavior, more concern about their appearance, and a preference for long rather than short hair, at this age, than controls. Exposure of high dosage and long duration was negatively related to both reports of discipline in school and influence over peers for females, while high dosage was associated with a preference for play in larger groups and disciplinary action for males. A negative relationship was found between activity level and both dosage and duration for boys and girls.

Regarding current behavior, significant differences were primarily found between progesterone-exposed males and their controls. These differences related to heterosexual activity and included less daydreaming about girls, less dating, less time spent thinking about marriage and family life, decreased incidence of going steady, and an increased likelihood of receiving disciplinary action in school.

Zussman *et al.* drew two major conclusions from their results. The first was "that progesterone *S*s are more studious and less socially interactive than controls . . . ." This hypothesis, they maintained, was "a more parsimonious and complete explanation for these data than a hypothesis of selective masculinization and feminization in different areas." The second conclusion was that "the evidence strongly supports the long-term influence of progesterone on the fetal brain, particularly with higher dosage, longer duration of administration, and early administration." These conclusions have to be taken very tentatively because of the lack of information given regarding the exposed sample and their controls.

Additional information related directly to school achievement was reported by Dalton (1976), who stated that "eleven of the 34 progesterone children obtained a university place compared with 2 normal controls and 1 toxemic control, that is 32 percent of progesterone children compared with 6 percent among all the control children ($p < 0.02$)." In comparison, the percentage of 18-year-olds entering universities in England was approximately 6% for both inner London and the borough from which most of the children had come. These results are similar to those obtained in the initial study of 10-year-old progesterone-exposed children (Dalton, 1968).

Estrogen

Of all the estrogens used for pregnancy maintenance, the synthetic diethylstilbestrol (DES) was perhaps the most widely administered, in part because of its inexpensiveness, its activity when given in oral form, and its potency: "five times that of estradiol if administered orally and only slightly less active if injected" (Noller and Fish, 1974). When the action of DES was

compared to that of the natural estrogens, their effects were found to be similar, and therefore

> In 1948 Smith recommended that DES be given for some of the complications of pregnancy, begining with 5 mg per day as early in gestation as possible, and that the dose be increased by 5 mg per day every 2 weeks and then every week up to 125 mg daily, and discontinued at the 35th week. The 1950 *Physician's Desk Reference* recommended this same dosage for threatened abortion, and as late as 1967 the *Physician's Desk Reference* recommended large amounts of stilbestrol for complications of pregnancy. (Lanier *et al.*, 1973)

It has been established that in the decade from 1945 to 1955 between 500,000 and 3 million women received DES (Noller and Fish, 1974), and Heinonen (1973) calculated that between 1960 and 1970 each year 33,000-100,000 children were exposed. Combining the estimates for 1945-1971 in the United States alone, approximately 980,000 to 4.5 million boys and girls were born of pregnancies treated with DES. In 1971 the Federal Drug Administration removed DES from the market because of the possible relationship between prenatal exposure and clear-cell adenocarcinoma of the cervix and vagina (Lanier *et al.*, 1973).

Given the large number of exposed individuals in the United States, it is curious that only one study of the possible psychological effects of prenatal DES and estradiol has been carried out (Yalom *et al.*, 1973). This investigation evaluated nondiabetic male offspring of diabetic mothers who received estrogen or DES in combination with progestin during pregnancy at the Joslyn Clinic in Boston. The two experimental groups included twenty 16-year-olds whose mothers received a combination of DES and hydroxyprogesterone acetate, and twenty 6-year-olds whose mothers were treated with estradiol and hydroxyprogesterone acetate. Both experimental groups were also divided by dosage and timing of estrogenic treatment. The control groups consisted of eight 16-year-old sons of diabetic mothers who had not received hormone treatment plus fourteen 16-year-olds of nondiabetic mothers matched for age and socioeconomic status. The contrast groups for the 6-year-old was made up of 17 subjects matched for age and socioeconomic status.

The results revealed that

> 16-year-old sons of hormone-treated diabetic mothers were less aggressive, less assertive, had less athletic skill and grace, and performed less well on the embedded figure task. Six year old experimental subjects were rated by their teachers as less assertive and poorer athletically than the normal contrast subject sample.

Interestingly, in most cases it was the nonexposed 16-year-old sons of diabetic mothers who were significantly more masculine than the DES-exposed 16-year-olds rather than the sons of untreated nondiabetic mothers. The authors suggested, albeit tentatively, that this finding indicated "it is not the diabetes but the hormone administration which influenced the psychosocial development to

move in the direction we have described." Analysis of the data on the DES-exposed older subjects showed a trend toward "low dose, late initiation of hormone to be related to 'feminine' behavior." There was no relationship between behavior and timing in the 6-year-olds, and the dosage/behavior relationship was in the opposite direction. The authors offered no explanation for these results.

There are a number of problems with this study: (1) The relationship among dosage, timing, and behavior could also have been interpreted as high dosage-early administration resulting in more masculine behavior. (2) The authors did not take into account the progestin administered because they suggested it did not represent any considerable increment in the amount of progesterone normally available to the fetus. However, it has not been ascertained how much of an increment *is* sufficient to produce an effect. (3) Most importantly, Yalom *et al.* stated:

> A major uncontrolled variable in the study was the state of health of the mothers in the experimental and contrast groups. The mothers of all the experimentals suffered from a chronic illness requiring daily attention. *Only eight of the 37 contrast mothers were also diabetic, and the severity of their diabetes was less.* It is possible that chronic illness in the mother induces overprotection of offspring or greater anxiety over health in offspring so as to interfere with aggressive masculine development. *It could also be that some endocrine disorder in diabetic women, irrespective of exogenous hormone administration, may have affected the fetal development of the boys.* (Italics added.)

Although certainty of interpretation cannot be assured from these data, the evidence on chronic serious diabetes renders the second hypothesis most parsimonious. For example, Jost (1973) described some of the effects on the fetus of maternal diabetes. This condition

> results in hyperglycemia, ketosis, and other maternal plasma changes. Hyperglycemia is reflected in the fetus and might be responsible for the fetal hyperinsulinism. Moreover, antibodies to insulin, when present in the maternal plasma, reach the fetus and inactivate fetal insulin.

Further, Forfar and Nelson (1973), in a paper discussing the efficacy of drugs during pregnancy, suggested that when evaluating the effect of a maternal drug treatment on the fetus one must consider that

> An association between the consumption of a drug during pregnancy and an adverse effect on the fetus does not necessarily imply causation. For instance, where illness in a pregnant mother has been treated with drugs, it may be impossible to differentiate a possible effect of illness on the fetus as opposed to a drug used to treat the illness.

Despite the above reservations, the finding of a relationship between "feminized" behavior and prenatal treatment with estrogen in human males is interesting in that it parallels the results of the investigations with animals.

RATIONALE FOR THE PRESENT INVESTIGATION

The present investigation was designed to look at cognitive and personality variables in a group of subjects exposed prenatally to exogenous steroids (progestins and estrogens), who had not been part of a hospital sample since birth and who might therefore be more representative of those millions of males and females in the general population having resulted from pregnancies in which such hormones were administered. The larger number of subjects and controls included in this study also allowed some design and statistical techniques which could not be utilized in the earlier studies with a smaller sample size. The study was further designed to minimize the problems in the studies mentioned above, such as the possibility of sampling bias, selection, and experimenter effects. The third purpose of this study was to test, on a different sample, the findings of Ehrhardt and Money (1967) and Dalton (1968) regarding IQ, with expansion of the data regarding long-term prenatal hormone effects on personality.

Socioeconomic status, genetic inheritance, parent education, and other familial factors were controlled by using all available siblings for comparison. Since performance on tests involving verbal reasoning is largely

> determined by genetic endowment, prenatal environment, and the physical and social environment after birth, data relating small differences in performance to obstetric events can be interpreted only against a control population matched for similar heredity, prenatal, and postnatal determinants. Therefore unless the differences are large, sibs provide the only possible controls. (Barker and Edwards, 1967)

Similar factors probably are operating with regard to personality development as well (Cattell *et al.*, 1970).

Experimenter effects were eliminated by employing examiners who were blind to the experimental plan and treatment category of the subjects they tested. In order to compile as complete a pregnancy and delivery history on the experimental subjects and control siblings as possible, all available information from every source including doctors and hospitals was collected, with particular attention to type of medication, dosage and duration of treatment, as well as prenatal and perinatal complications.

METHODS

Sample Selection

To study the effects of prenatal treatment with steroid hormones on human intelligence and personality using a design which provided the most stringent experimental controls possible, a minimum of 50 families were sought in which the mother had been treated during at least one pregnancy with synthetic pro-

gestin and estrogen. Further, each family had to include for comparison at least one sibling from the same parents whose gestation was not at risk and therefore was not treated with hormones. An effort was made to test every child of a sibship should more than two children be available. Subjects had to be at least 4 years of age so that IQ testing could be carried out with the Wechsler IQ tests. It was projected that a minimum population of 500 treated pregnancies was needed in order to attain adequate sample size.

The records from two private Los Angeles clinics specializing in obstetrics and gynecology and from one private physician supplied the population of cases from which the 56 familes composing the present sample were identified. In addition to the criteria for inclusion mentioned above, treatment during pregnancy had to conform to a minimum of 4 weeks of hormone administration during the first two trimesters. Six hundred records were read in order to identify the 56 subject families who made up the sample. These families included 155 offspring, of which 141 were tested. The remaining 15 were either unavailable, too young, or not of the same two parents.

Every family contacted for inclusion in the study consented to participate. All hospital and doctor's records on the pregnancies of every child to be included were sought. Final participation required pregnancy and delivery records for each child exposed and unexposed. Sixty private physicians and 83 hospitals furnished the records necessary to evaluate and provide information on the pregnancies and deliveries of the 141 subjects.

Sample Description

Families

The sample included 56 families from the Los Angeles, San Diego, and San Francisco areas. Thirty families had two children tested. There were 23 families in which three children were tested, 11 having one exposed subject and 12 having two exposed subjects. Three families included four tested children of whom two were exposed and two unexposed. Social class as determined by the Hollingshead ratings (1957) revealed that the majority of the 56 families were in the two highest classes designated, I and II, with ten and 33 families, respectively. Eleven families were found to be in class III and two in the fourth category. None was in the fifth class. These ratings are based on father's occupation, income, and education. Therefore, the sample as a whole was in the majority from the upper middle class.

Treatment Groups and Medications

The mothers and the children were treated with hormones during pregnancy for a number of reasons. The major indications for treatment were (1) threatened

Table I. Criteria for Selection of Index Cases into Three Treatment Subgroups

Treatment subgroups	Range of total dose[a]		Ratio[a]	
	Progestin	Estrogen	Progestin to Estrogen	*N*
Estrogen (E_p)	478-5,611	3,500-13,905	>1:1.5 1:9-1:1.5	16
Progestin[b] (P_e)	525-9,890	4-40	>100-1 100:1-358:1	26
Mixed (M_{pe})	490-10,650	6-1,390	<100-1 3:1-82:1	29

[a] Reported in milligrams.
[b] Seventeen subjects received no estrogen.

miscarriage, (2) difficulty in conceiving and therefore in supporting a long-awaited pregnancy, (3) a history of miscarriage, even if this particular pregnancy evidenced no complications, and (4) various other complications of pregnancy (see Table VII).

The children of these treated pregnancies and their unexposed siblings were partitioned in two ways: (1) two groups composed of all treated subjects and all untreated subjects (treatment groups) and (2) three treatment subgroups selected by the ratio of progestin to estrogen administered. These three subgroups were designated as the estrogen group (E_p), whose members were exposed to the highest amounts of estrogenic hormones and the lowest dosages of progestin; the progestin group (P_e), in which children were exposed to intermediate dosages of progestin and the lowest amounts of estrogen with the majority of the group receiving no estrogen at all; and the mixed group (M_{pe}),

Table II. Duration and Total Dosage of Progestin and Estrogen Treatment in Hormone-Exposed Group

Drug	Range	Mean	Median	*N*
Progestin				
Duration in weeks	3.97-36.08	17.03	15.95	71
Dosage in milligrams	478-10,650	2779.75	1857.50	71
Estrogen				
Duration in weeks	0-34.22	13.36	10.53	71
	0.14-34.22	17.57	16.59	54[a]
Dosage in milligrams	0-13,925	1495.36	58.25	71
	4-13,925	1966.13	247.50	54[a]

[a] Data with 17 subjects receiving no estrogen eliminated.

who were exposed to the maximum dosages of progestin and intermediate amounts of estrogen.

Table I gives the range of the total dose of progestin and estrogen and the ratio of progestin used as criteria for inclusion in each subgroup. Table II describes range, mean, and median of treatment duration in weeks and total dosage of progestin and estrogen in milligrams for the exposed group.

The mothers of 17 subjects received no estrogen during pregnancy (Tables I and II). These subjects are all found in the P_e group. All mothers of the subjects in both the E_p and M_{pe} groups were treated with a combination of progestin and estrogen.

Table III lists the medications administered during the 71 treated pregnancies. Seventy-one of the women whose pregnancies were designated as treated received at least one medication, 59 at least two, 43 at least three, 20 at

Table III. Medications Given to Mothers of Hormone-Exposed Group During Pregnancy ($N = 71$)[a]

Drug			N^f	Drug	N^f
Progestins				Additional estrogens[d]	
Broxorone (Squibb)			1	Allyl Estranol (Organon)	2
Colprosterone[e]			13	Amestrogen (Squibb)	1
Deladroxate	110	(Squibb)	4	Delestrogen (Squibb)	8
Deladroxate	130	(Squibb)	6	Estrone[a]	1
Deladroxate	150	(Squibb)	5	Hexestrol[e]	1
Delalutin	142	(Squibb)	29	Mestranol[e]	1
Delaxadrone		(Squibb)	1	Stilbestrol[e]	17
Deluteval[b]		(Squibb)	24		
Depo-Provera		(Upjohn)	2	Total	31
MK665[c]		(Merck) ethymerone	1		
19NET, Norlutin		(Syntex)		Other drugs	
Norlutin Acetate		(Parke Davis)	13		
Norethynodrel[b]		(Searle)	2	Thyroid (Armour)	4
Pranone (Schering)			3	Cytomel (Smith, Klein & French)	7
Provera (Upjohn)			15	Methergine (Sandoz)	2
Provest[b] (Upjohn)			10	Prednisone (McKesson)	2
RS1280[c,e] (progestogen)			2	Proloid (Warner-Chilcott)	1
SC4641[c] (Searle)		19 NET	1	Sterane (Pfizer)	5
SC4642[c] (Searle)		norethynodrel	2	Synthroid (Flint)	5
SC9022[c] (Searle)		methylnortestosterone	2		
SC10230[c,g] (Searle)			1		
SC11800[c] (Searle)		ethyndiol	1		
142.53[e]		aqueous progesterone	1	Total	26
			139		

[a] Many mothers received more than one drug.
[b] Compounds that have estrogens included.
[c] Experimental compounds.
[d] Not including estrogen found in combination with progestin.
[e] Company not identified.
[f] Number of pregnancies in which medication was administered.
[g] 21-Fluoro-17-hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate.

least four, and eight received five of the listed medications during pregnancy. As can be seen, treatment regimes were not consistent with regard to dosage, duration, and combination of hormones administered.

Subjects

The number of male and female subjects by treatment group and subgroup is given in Table IV. There were 26 exposed males and 27 unexposed males, 45 exposed and 43 unexposed females. The total number of untreated siblings when arranged by subgroup is greater than by treatment group. This is due to uneven family compositions so that in those families composed of more than one exposed subject and only one unexposed sibling the unexposed child appears more than once. Age of subjects by treatment group and subgroup is shown in Table V. In the exposed subjects, age at time of testing ranged from 5 to 17 years and in untreated subjects from 4 to 21 years. The mean age for all groups and subgroups ranged from 10.61 to 12.46 years.

Birth order by sex and treatment group is given in Table VI. Children in the exposed and unexposed groups were almost equally distributed with 29 firstborns in the exposed group and 23 in the unexposed group. Forty-two exposed children were latterborns, including positions 2 through 5, in com-

Table IV. Sex of Subjects by Treatment Group and Subgroup

	Sex		
	Males	Females	Total
Group			
Exposed	26	45	71
Unexposed	27	43	70
Total	53	88	141
Subgroup			
Estrogen (E_p)			
Exposed	5	11	16
Unexposed	2	11	13[a]
Progestin (P_e)			
Exposed	10	16	26
Unexposed	16	13	29[a]
Mixed (M_{pe})			
Exposed	11	18	29
Unexposed	14	19	33[a]

[a] Untreated *n*'s in subgroups are not equal to those found in two groups because of the repeated use of an untreated sibling when more than one treated subject resided in a family.

Table V. Age of Subjects at Time of Testing by Treatment Group and Subgroup

	Range[a]	Mean	*N*
Group			
Exposed	5-17	11.23	71
Unexposed	4-21	11.29	70
Total	4-21	11.26	141
Subgroup			
Estrogen (E_p)			
Exposed	6-15	12.06	16
Unexposed	8-16	11.81	13
Progestin (P_e)			
Exposed	5-17	12.46	26
Unexposed	6-18	11.81	29
Mixed (M_{pe})			
Exposed	6-18	10.61	29
Unexposed	4-21	12.12	33

[a] Age in years.

parison to 47 latterborns in the unexposed group. However, the exposed group had more secondborn subjects whereas the unexposed group contained more children in the third position.

Prenatal and Perinatal Complications

Prenatal complications, including notes by the attending physician indicating serious problems (i.e., retroverted uterus, long periods of bed rest, etc.), in the treated and untreated pregnancies are listed in Table VII. Information on the description of the placenta was recorded separately. In the treated group, 37 women suffered at least one complication during pregnancy, 26 women had at least two, and 16 women had three. For the untreated pregnancies, 17 were reported to have had at least one complication and six had two. None was

Table VI. Birth Order by Treatment Group and Sex

	Exposed			Unexposed		
Sibling position	Male	Female	*N*	Male	Female	*N*
1st	9	20	29	9	14	23
2nd	14	21	35	7	14	21
3rd	2	4	6	9	13	22
4th	1	–	1	2	1	3
5th	–	–	0	–	1	1
Totals	26	45	71	27	43	70

Table VII. Prenatal Complications Reported by Physicians During Pregnancy by Treatment Group

Complication[a]	Exposed ($N = 71$) 1	2	3	Total	Unexposed ($N = 70$) 1	2	3	Total
	Prenatal							
Anemia	0	0	0	0	1	0	0	1
Bed rest[b]	2	6	1	9	0	0	0	0
Bleeding[c]	23	15	5	43	10	2	0	12
Bloody urine	0	0	0	0	0	1	0	1
Cramps (serious)	4	1	3	8	1	0	0	1
Edema	3	2	4	9	1	1	0	2
Hypertension	0	0	1	1	0	0	0	0
Incompetent cervix	1	1	1	3	0	0	0	0
Nausea (severe)	1	0	0	1	0	0	0	0
Premature labor	1	0	1	2	1	0	0	1
Retroverted uterus	1	0	0	1	0	0	0	0
Toxemia	0	0	0	0	2	0	0	2
Weight gain (excessive)	1	1	0	2	1	1	0	2
Viral meningitis	0	0	0	0	0	1	0	1
Subtotal	37	26	16	79	17	6	0	23
	Placenta[d]							
Focal sclerosis				1				
Foamy				–				1
Many infarcts				1				
Large				1				–
Previa				–				1
Twin				2				–
Total				84				25

[a] A total of a maximum of three possible complications could be recorded for each pregnancy.
[b] "Bed rest" indicates the severity of pregnancy complications and was recorded only when the patient was confined to bed for more than 1 week.
[c] Bleeding could be recorded more than once per woman if it occurred in more than one month.
[d] Information on the condition of the placenta was recorded separately.

recorded as having had three complications. A total of 79 prenatal complications were noted for the treated pregnancies, with five placentas recorded as unusual. In the untreated group, there were a total of 23 complications and two reports of unusual placentas. Table VIII lists the perinatal complications found in the treated and untreated pregnancies. There were 35 recorded for the deliveries of treated pregnancies and 25 for the untreated pregnancies.

Table VIII. Perinatal Complications Reported by Physicians During Pregnancy by Treatment Group

Complication	Exposed (N = 71)	Unexposed (N = 70)
Artificial rupture of membranes	4	8
Breech	5	1
Cesarean	5	0
Cord around neck	2	1
FHT slowed[a]	2	0
Induced	4	6
Premature[b]	6	1
Premature rupture	2	2
Prolapsed cord	1	1
Prolonged labor	2	1
Placenta		
Abruptio/ablatio	1	0
Adherent	1	2
Retained	0	2
Total	35	25

[a] Fetal heart tone.
[b] Prematurity could be classified as a prenatal complication.

Selection of Tests

Intelligence Tests

A series of standard intelligence measures, the Wechsler Intelligence Scales, were chosen for administration because of their inclusion in many previous investigations (Baker and Ehrhardt, 1974; Ehrhardt and Money, 1967; Lewis *et al.*, 1968; Masica *et al.*, 1968; Money, 1972a). The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) was given to subjects 4 years of age (N = 2), the Wechsler Intelligence Scale for Children (WISC) to the 124 subjects between 5 years and 15 years 11 months, and the Wechsler Adult Intelligence Scale (WAIS) to the 15 subjects who were over 16 years of age. All 141 children were tested. This series of measures was also selected because scores can be compared over a wide age range, a necessity when evaluating siblings. From all three scales, three standard scores were obtained. The Full Scale IQ is the measure of general intelligence. The Verbal IQ is a score generated from the six subtests dealing with verbal, number, and memory abilities. The Performance IQ is composed of six visual-motor tasks. These scores have a mean of 100 and a standard deviation of 15 in the general population. An additional analysis was done by the factor-analyzed clusters of subtests found by Cohen (1955, 1959).

The Verbal Factor includes four subtests from the Verbal Score (Information, Comprehension, Similarities, and Vocabulary), and the Perceptual Factor is loaded by two Performance subtests (Block Design and Object Assembly).

Personality Tests

Similar to the requirements for the intelligence measure, a series of personality tests were sought which would have comparability of scores across a wide range of ages from early childhood to late adolescence. The Cattell Personality Questionnaires were chosen because they are designed so that children from 6 years of age through adulthood can be compared. These tests fulfilled the additional requirements of focusing on components of normal healthy personality development rather than the pathological aspects, and evidencing high reliability as expressed in both dependability coefficients and stability coefficients (Cattell *et al.*, 1970).

The Early School Personality Questionnaire (ESQP) was administered to subjects 5 years 11 months through 7 years of age (N = 22), the Children's Personality Questionnaire (CPQ) to subjects 8-11 years of age (N = 50), the High School Personality Questionnaire (HSPQ) to subjects 12-17 years of age (N = 61), and the 16 Personality Factors (16 PF) to subjects 18 years and older (N = 6). The two children who were under 5 years of age were not tested. For subjects administered the ESPQ, the tester read the questions and recorded the children's responses. Children taking the CPQ were checked for reading comprehension and, if they were able, took the test themselves. Otherwise, it was adminstered by the tester. All HSPQs and 16 PFs were self-administered.

Thirteen primary factors are generated from the ESPQ, 14 factors from the CPQ, and 16 factors from the HSPQ and 16 PF. These primary factor source traits are expressed as dimensions in bipolar form. The 12 factors on which analyses were carried out were those which the four questionnaires generally had in common and for which a large enough number of subject pairs were available. From the primary factors, four second-stratum factors are derived. They include Anxiety, Extroversion, Tough Poise, and Independence. Cattell *et al.* (1970) described the second-stratum factors "as broader influences or organizers contributing to the primaries and accounting for their being correlated."

Data Analyses

The most serious problem confronted in the investigation of the effects of a prenatal intervention on human development is the impossibility of designing the study with the most fundamental component of true experimental design. Random assignment of subjects to the experimental and control groups

prior to the administration of treatment is precluded by the legal and ethical constraints on treating healthy mothers and fetuses with drugs whose efficacy is not proven and may even be harmful to one or both. The limitations placed on the interpretation of results obtained through a design which does not employ random assignment to groups and uses instead some form of matching are obvious. However, there are two methods, applied in this investigation, which when used simultaneously allow for more confidence in the interpretation of results obtained from such designs based on human retrospective data. The first is the utilization of unexposed or unaffected siblings as the comparison groups. Siblings provide the best available preexperimental strategem for matching on heredity and environment. The second method is the *post hoc* application of various statistical controls which, although they do not produce as strong a basis for the inference of causal relationships, do provide more confidence in consequent interpretations of the data.

Following a series of analyses comparing all exposed with all unexposed subjects from which no significant results were obtained, it became clear upon closer inspection of the treatment information that the combinations of hormones administered were not similar. Contrary to a preexperimental assumption, physicians treated women evidencing at-risk pregnancy with hormone regimes that varied considerably not only among doctors but also among individual patients treated by the same doctor. As was noted, some women were administered as many as five different hormone preparations during a single pregnancy. Therefore, hormone treatments were segregated into three relatively distinct treatment subgroups: estrogen (E_p), progestin (P_e), and mixed (M_{pe}) (as described in Table I). Exposed subjects were placed into these three subgroups along with the three groups of their matched siblings dependent on the ratio of progestin to estrogen administered. When more than one unexposed sibling was available, mid-sib score was used for comparison. When more than one exposed child was tested in a family with only one unexposed sibling, then the sibling appears in each comparison group to which the exposed cosiblings were assigned. Subsequently, a second series of analyses was performed on the raw scores and on difference scores generated by subtracting the unexposed sibling or mid-sib score from the score of the exposed cosibling within the same family. On both sets of scores, analyses of covariance (ANCOVA) were performed using a $3 \times 2 \times 2$ design with three levels of treatment (estrogen, progestin, and mixed), two levels of total dose (low level and high level), and two levels of sex of treated subject (male and female). When it was impossible to extend the study until only all male or female pairs of treated and untreated siblings were found, mixed-sex pairs were accepted. Covariates included sibling score, prenatal complications, and perinatal complications. Difference scores were analyzed by an ANCOVA with both prenatal and perinatal complications as covariates, and *t* tests were used to evaluate the magnitude of the differences themselves. Comparisons between means in the significant interactions were analyzed by Duncan's new multiple range statistic (Duncan, 1955).

RESULTS

IQ

No significant results were obtained from any of the analyses performed on the five IQ scores generated by the Wechsler IQ tests when comparing either treatment groups or paired siblings within a group. The addition of covariates did not alter the results. When raw IQ scores were adjusted for the influence of sibling performance, no difference among hormone treatments, dose level, sex, or their interactions for any measure was demonstrable. Similar null results were obtained with the addition of prenatal and then perinatal complications.

The performance on IQ tests of males or females exposed to various admixtures of hormones at various dosage levels *in utero* appears unaltered by treatment and largely independent of prenatal and perinatal complications. The best predictor for the later IQ scores of exposed subjects was the IQ score of the subjects' unexposed siblings. The average full scale IQ for treated subjects over all hormone treatments was 121.85 as compared to their untreated siblings' mean score of 119.92. These scores are 20 points higher than the norm for the United States. This elevation can be explained most parsimoniously as related to the high socioeconomic status of these families.

Personality

Although no significant results were obtained by any analysis on the IQ scores, significant results were found on two of the second-order factors and four of the primary factors from the Cattell Personality Questionnaires. The subjects in the P_e group and the E_p group were most different from each other, with the M_{pe} group subjects lying in an intermediate position. The P_e group members (treated with intermediate amounts of progestin and the minimum dosages of estrogen) were more independent, individualistic, self-assured, self-sufficient, and sensitive and less cortertic[3] on the questionnaires, whereas the E_p group members (minimum amounts of progestin with maximum dosages of

[3]Cattell *et al.* (1970) define the dimension cortertia vs. pathemia as follows:

> The "positive" pole is called cortertia, as an abbreviation of "cortical alertness." This is consistent with the findings that high U.I. 22 goes with quick reaction time, short flicker fusion, high alpha wave interruption in EEG, and other signs of high cortical activation level. . . . It is, however, a consistent personality *trait,* not a state of activation. . . . The ratings which go with cortertia are those of cheerfulness, alertness, and readiness to handle problems at a "dry," cognitive, objective level, whereas those at the pathemic pole, as the name indicates, operate at a mood level. . . . Low scoring (pathemic) individuals show a tendency to *feel* rather than to *think.*

Table IX. Progestin (P_e), Estrogen (E_p), and Mixed (M_{pe}) Group Means for Six Personality Factors[a]

Treatment subgroup	Personality factors					
	Cort.	Ind.	I	J	O	Q_2
P_e	4.98	7.30	6.75	7.82	2.54	6.70
E_p	5.84	5.13	5.28	4.04	5.07	3.11
M_{pe}	6.26	5.49	4.54	5.24	4.66	6.14
	M_{pe} and $E_p > P_e$[b]	$P_e > E_p$ and M_{pe}[b]	$P_e > E_p$ and M_{pe}[b]	$P_e > E_p$[b]	$P_e < E_p$[b]	P_e and $M_{pe} > E_p$[b]

[a]Mean scores of P_e, E_p, and M_{pe} on six factors for the Cattell personality questionnaires which yielded statistically significant between-groups differences. The factors are bipolar dimensions with the high-score pole vs. the low-score pole for each as follows: Cort., dry cognitive style vs. dependence on feeling; Ind., independent vs. subdued; I, sensitive vs. tough-minded; J, individualistic vs. group oriented; O, insecure vs. self-assured; Q_2, self-sufficient vs. group-dependent. The possible range in which an individual's score can fall is 1-9, with the norm by age and sex set at 5.

[b]$p \leq 0.05$.

estrogen) were more group oriented, group dependent, and cortertic and less independent, sensitive, and self-assured.

Profile of Personality Factors by Treatment Regime

Table IX shows the significant results on the second-order and primary factors for the three treatment subgroups. The relationships of the subgroup means to each other and the norms of the Cattell questionnaires are graphically represented in Table X. In answering the questionnaires, subjects from the P_e group demonstrated a consistent pattern of significant findings, representing themselves as more independent, more individualistic, more self-assured, and more self-sufficient. They were also more sensitive and less cortertic than the E_p and M_{pe} groups. In terms of the group profiles generated from the questionnaires, the P_e group subjects and E_p group subjects were the most different from each other (see Table X). From their questionnaire data, E_p group members can be described as more group oriented, more group dependent, less independent, less self-assured, and less sensitive. They also showed more cortertia. Demonstrating an intermediate pattern of responses in comparison to the P_e and E_p groups

Table X. Personality Profile by Treatment Subgroup

	Personality factors							
			I	J		O		Q_2
Treatment subgroup	Cortertic	Independent	Sensitive	Group oriented	Individualistic	Self-assured	Group dependent	Self-sufficient
Progestin (P_e)	↓[b]	↑[a]	↑		↑	↑		↑
Estrogen (E_p)	↑	↓	↓	↑		↓	↑	
Mixed (M_{pe})	↑	↓	↓					↑

[a] More: ascending arrows signify a significant difference in which the subgroup members were significantly different from one or both of the other groups and the group mean was above or below the questionnaire norms.

[b] Less: descending arrows signify a significant difference in which the subgroup members were significantly different from one or both of the other groups but the group mean was at or near the questionnaire norms.

Table XI. Group Mean Difference Scores on Six Personality Factors[a]

	Personality factors					
Subgroup	Cort.	Ind.	I	J	O	Q_2
P_e	−0.60	+1.19[b]	+0.37	+1.39[b]	−1.03[b]	+2.93[b]
E_p	+0.64	−0.50	−0.65	−1.40[b]	−0.06	−3.67[b]
M_{pe}	+0.28	−0.17	−1.13[b]	+0.03	−0.16	−0.16

[a] Mean difference scores of P_e, E_p, and M_{pe} groups on six factors from the Cattell Personality Questionnaires (see footnote to Table IX for explanation of factors). A difference score is derived by subtracting the score of the unexposed sibling from the score of the exposed sibling. Individual scores were adjusted for pre- and perinatal complications prior to the generation of pair differences. A positive score indicates that the exposed subject received a higher score than the unexposed sibling.

[b] $p \leq 0.05$ for exposed vs. unexposed siblings.

was the M_{pe} group, which, like the E_p group showed more cortertia, less independence, and less sensitivity, and like the P_e group more self-sufficiency.

The consistency of the P_e group profile was supported when the results of the difference scores analyses, revealing the differences between exposed subjects and their unexposed siblings, were considered (Table XI). The subjects exposed to the P_e group regime were more independent, more individualistic, more self-assured, and more self-sufficient than their unexposed siblings. This profile of significant findings on the factors was in agreement with the P_e group findings on the three exposed groups of subjects for four of the five factors, whose means fell above or below the questionnaire norms, and was not inconsistent on either of the remaining two factors. The subjects exposed to the E_p group regime were less individualistic and less self-sufficient when compared to their untreated siblings. These results were not inconsistent with the treatment subgroup comparisons, but they were not identical or as strong: less individualistic rather than more group oriented and less self-sufficient rather than more group dependent. Although these findings for the comparisons between E_p group exposed and unexposed siblings were not as substantial as the differences found between the treatment subgroups, the direction of the effect was consistent and the differences between the P_e and E_p subjects were maintained. When M_{pe} group exposed subjects were compared with their exposed siblings, they were revealed as less sensitive. This finding matches one of the two found when the treatment subgroups were compared. A reasonable interpretation integrating the configuration of significant factors obtained for the P_e and E_p groups is to characterize P_e group treated subjects as "inner" or "self" directed, which coordinates the findings of more sensitivity and less cortertia with the other results. The E_p group findings can then be interpreted as representative of "outer" or "other" directedness.

It is not surprising that the characterizations of subjects in the E_p and P_e groups were the most disparate since the treatment regimes for these two groups were most dissimilar: the members of the P_e group received little or no estrogen while not only had the E_p group received the most estrogen but also each subject was exposed to higher dosages of estrogen than progestin. Furthermore, the high level of consistency in personality findings observed across analyses for the P_e group may be related to the fact that this group received the most uncomplicated hormone regime. As discussed above, the mothers of 17 members of the P_e group received *only* progestin therapy with *no* estrogen treatment while the remaining subjects were exposed prenatally to only 4-40 mg of estrogen during the entire period of gestation in combination with the progestin.

There is also evidence, reported elsewhere (Reinisch, 1977), suggesting that the P_e group subjects demonstrated a configuration of personality scores on the Cattell tests predictive of elevated school achievement and success (Cattell *et al.*, 1970).

DISCUSSION

IQ and Prenatal Hormone Effects

The data from this investigation provide no significant differences between hormone-exposed subjects and their unexposed siblings on the IQ tests even when the means of total steroid dosage level for the various subgroups of subjects ranged from 2999 to 7553 mg per offspring and the preparations administered ranged from pure synthetic progestin to nearly equal mixtures of both progestin and estrogen. It is possible that one of the various progestins administered had an elevating effect on IQ. Unfortunately, there were not enought subjects treated with any one hormone or in similar combinations to analyze this possibility.

The finding that untreated sibling scores are the best predictors of treated offspring IQs is consistent with the IQ literature on the correlation of IQs among sisters and brothers (Conrad and Jones, 1940; Erlenmeyer-Kimling and Jarvik, 1963; Hildreth, 1925; Maxwell and Pilliner, 1960; Roberts, 1940; Thorndike, 1928). These studies of the relationship between siblings on IQ all obtained correlations of between 0.40 and 0.60. The correlation between sibling IQs in this investigation is very similar (Full Scale IQ score $r^2 = 0.2076$, $r = 0.46$).

The finding of no differences in IQ between siblings is identical to the results of the only other family study on prenatal hormone exposure in adrenogenital syndrome and IQ in which unaffected siblings and parents were used as the comparison groups (Baker and Ehrhardt, 1974). However, the excess hormones in that investigation were of an endogenous origin rather than exogenously

introduced as is the case in this investigation. The only other study of children treated with hormone preparations similar to those found in this study is the 1967 investigation of progestin-induced female hermaphrodites by Ehrhardt and Money. The limitations of this study have already been discussed; nevertheless, there is, perhaps, an important difference in the samples used in these two studies. Nine of the ten girls in the Johns Hopkins report were masculinized morphologically by the prenatal hormone treatment. None of the subjects in the present study was so affected. It is possible that the exogenously introduced hormones given to the mothers in both these investigations positively affected IQ only in children who were particularly sensitive to them. This fetal sensitivity might be signaled by the influence of the hormones on the genitalia. In other words, perhaps IQ is elevated only in children whose genitalia are also affected by the hormones, and not in exposed children who do not show genital masculinization. However, the fact that the average IQ for this sample was 121 and that of the ten masculinized girls was 125 renders this hypothesis less plausible.

The results of the present investigation indicate that synthetic progestins and estrogens administered during pregnancy are neither detrimental nor beneficial to later mental development as measured by standardized IQ tests.

Personality and Prenatal Hormone Exposure

As there were no significant differences in IQ among any of the groups, the samples are therefore matched for IQ when considering the personality findings. A second point is that the effects found on the dimensions of personality are not assumed to be directly influenced by the prenatal treatment with hormones. Any effects that the introduction of excess or novel hormones might have are assumed to be of a basic nature affecting temperament or dispositional traits which, in turn, relate to the development of a personality type. As Goy pointed out in 1970, when considering the dependence of the human species on experience and learning processes for the expression of complex patterns of behavior, the influence of the prenatal hormones is best understood as setting a bias on the neural substratum, which in turn predisposes the individual to the acquisition and expression of particular patterns of response and behavior.

It is not unexpected that a difference in personality would exist between hormone-exposed and unexposed siblings as well as between treatments. The animal research of the last decade and a half indicates that early exposure to hormones, whether from an endogenous or exogenous source, affects a wide range of behaviors including activity level, social interaction, curiosity, emotionality, dominance, and aggression. The behavioral dimensions found to be related to early hormone exposure in animals might well be expressed in humans in terms of preferences for group activity and a dependence on peer opinion and behavior vs. an individualistic, self-sufficient style as reflected in the responses

on the personality questionnaire. The way in which an individual views him- or herself and therefore presents him- or herself on a pencil-and-paper questionnaire must relate, in some way, to the person's behavior, personality style, and life choices.

The configuration of personality findings obtained in relation to the P_e group corresponds well to the 1967 findings of Ehrhardt and Money. In their study, when inquiry was made of the mothers of progestin-treated female offspring regarding their dependency and self-assertive behaviors, a high frequency of self-assertive independence and self-reliance was reported and a correspondingly low frequency of dependency and demand for succorance. These judgments are very similar to the findings in this sample of more independence, individualism, self-sufficiency, and self-assuredness.

The characterization of the configurations of personality scores obtained for the P_e group and E_p groups as "inner" or "self" directed and "outer" or "other" directed, respectively, seems more open-ended at this still early stage of the investigation of the effects of prenatal hormone exposure on humans than using the culturally sterotyped concepts of masculinity and femininity. Perhaps these sex-related terms could be justified when comparing independence, individualism, and self-sufficiency with group orientation and group dependence. However, tempting as that might be, the finding of higher sensitivity in the P_e group does not fit the generally held stereotype, whereas it does conform to the idea of being self-directed rather than group influenced. A puzzling factor in the configuration of scores found for these two groups is the finding of higher cortertia for the E_p group, with the P_e group falling on the norm, since this factor may seem in contradiction to the rest of the personality findings for the E_p group. However, Cattell *et al.*'s (1970) definition of this dimension states that clarification of the meaning of this factor still needs further confirmation. If "inner" directedness is seen as also connoting being in touch with one's feelings, needs, and desires and being "outer" directed as perhaps being less connected to, or responsive to, one's inner stirrings, then cortertia defined as a dry cognitive style with less tendency to feel becomes a more coherent aspect of the "outer" or "other" directed individual's personality. The progestin group subjects whose scores reside on the mean would then be understood to have more access to their feelings than the estrogen group subjects and to therefore be able to "handle problems on a dry cognitive, objective level" (Cattell *et al.*, 1970) as well as to have more access to the emotional parameters of a situation when appropriate.

These findings of differences in personality between exposed subjects and their unexposed siblings and the differences between groups of treated subjects await further verification and support from future investigations including more diverse methods and data. Allowing for unsystematic prescribing of these preg-

nancy-maintaining drugs in both amount and kind, and allowing for the limitations of a pencil-and-paper test, these findings strongly suggest a relationship between prenatal treatment with hormones and personality. It is certainly premature to infer a treatment-specific relationship between personality type and the different treatment regimes. However, the results rather strongly suggest that a relationship does exist which might be elucidated by additional interview and observational data from larger samples.

GENERAL DISCUSSION

Hormones and Pregnancy Maintenance

Although progesterone, synthetic progestins, and estrogen are administered to pregnant women for the purpose of maintaining gestations which are considered clinically to be at risk, hormone therapy has not been proven to support precarious pregnancies. In animal experiments on pregnancy maintenance, the efficacy of prenatal treatment with progesterone and synthetic progestin in rats, pigs, and sheep has not been shown to be beneficial, and it has even been suggested that treatment can adversely affect the maintenance of the pregnancy (Nalbandov, 1958). Three Danish investigations of short-term treatment with progestins of mothers evidencing threatened miscarriage showed no significant differences between treated and untreated mothers (Fuchs and Stakeman, 1960; Møller and Fuchs, 1965; Øvlisen and Iversen, 1963). However, these women were treated for a much shorter duration than is traditional in the United States. A study of the effectiveness for pregnancy maintenance of one of the hormone preparations administered to women in this study in which administration was similar in dosage, timing, and duration was done in Australia (Shearman and Garrett, 1963). In this double-blind study, there were no differences in the salvage rate of fetuses between the treated and placebo groups. Finally, with regard to estrogen therapy, Noller and Fish (1974) in a discussion and review of the use of DES and natural estrogens concluded:

> Though no evidence has been collected so far to condemn natural estrogens, the lack of substantial evidence for benefit from administration of any estrogen in pregnancy makes their use questionable. The statement that there is presently no indication for the administration of estrogens during pregnancy is probably true.

It seems, therefore, safe to assume that whatever effect on the fetuses the hormones administered to the women in this investigation had, they did not help to provide a "better" or more "friendly" fetal environmental and the effects on personality obtained are not the product of an improved uterine climate.

Fetal Wastage of Males

Note in Table IV the much lower number of males than females in the sample. The attrition in the number of males is equally evident in both the exposed and unexposed groups. This high wastage of male fetuses and the ensuing lower number of males born are surprising only in the final ratio of males born. It is expected that more males than females will die during gestation since it has been shown that approximately 140 males are conceived to every 100 females, whereas at birth the ratio will be approximately 105:100. However, as can be seen, the expectation is that more males than females will be born despite the higher male wastage. The implications drawn from both the normal population and this sample are that males have lower survival potential in general, and in adverse uterine environments in particular. Inspection of the data on pre- and perinatal complications in Tables VII and VIII leads to the conclusion that the uterine environment provided by these mothers for the majority of fetuses was far from optimal.

A similar imbalance of male to female offspring was observed in the family study of the adrenogenital syndrome (Baker and Ehrhardt, 1974; Ehrhardt and Baker, 1974). It is not possible to ascertain, at this time, whether the causes of augmented fetal wastage of males in these two studies are similar. Nevertheless, these findings provide additional evidence for the concept of a generalized male vulnerability (Money, 1972b). Furthermore, the fact that the number of males was decreased in both the exposed groups and the unexposed sibling groups renders this finding inconsequential with regard to the significant personality results obtained in this investigation.

Birth Order and Treatment or Nontreatment

It might be surprising to some that there are nearly equal numbers of firstborn and latterborn offspring whose gestations were treated or untreated However, this finding is in agreement with those of other samples (Bongiovanni *et al.,* 1959; Wilkins *et al.,* 1958), and, therefore, treatment does not seem to be correlated with a particular birth order.

Maternal Knowledge of Treatment and Postnatal Effect on Offspring

It might be assumed that maternal knowledge of special medical treatment could affect the manner in which a mother treated her child after birth, that perhaps the child of a treated pregnancy would receive special maternal attention and care after birth and throughout development – different from that of other offspring – and that this special treatment would in turn produce differences between exposed and unexposed children. Despite the fact that the different hormone treatments have been shown to have different effects which

would be difficult to explain in terms of maternal caretaking, there is additional evidence to suggest that some factor related to maternal knowledge and subsequent caretaking is not of significance in the results obtained. Many of the mothers in this study, when called in order to solicit the participation of their families in the investigation, responded by saying that they would love to participate but that they were sure they had taken no medication during pregnancy, save vitamins. In all these cases, the mothers had been treated with hormones during pregnancy – some had received as many as two intramuscular injections per week. Although this lack of knowledge or loss of memory may seem unusual, Noller and Fish (1974) report a similar situation in their DES investigation:

> Questioning of the mother is not sufficient to rule out DES therapy. In our series of cases, few mothers remembered taking hormone preparations and several who claimed they "never took any pills" while pregnant were found to be in error on review of the prenatal history.

Even in the extreme case when the effect of a prenatal event is as obvious as a major change in genital morphology like that found in girls with the adrenogenital syndrome and progestin-induced hermaphroditism, the effect on the parental attitude toward the child and her behavior is difficult to predict:

> In the two groups with fetal masculinization, the parents' knowledge of their daughter's genital abnormality at birth may have influenced their reactions toward their daughter's behavior in different ways. Some parents may have accepted it; others may have attempted to discourage it. We found, however, no consistent difference in parental attitude toward their daughter's behavior between patient and control groups (Ehrhardt, 1973)

Furthermore, it must be noted that in this sample the untreated pregnancies had their share of difficulties too, and in general few of the pregnancies were free of problems. From the above evidence, it seems unlikely that the fact that a mother knew she was treated, in and of itself, had a significant effect on her subsequent treatment of that offspring as compared to the siblings born of untreated pregnancies.

Drug Effects in Pregnancy

Although it is generally accepted now in medicine that the fetus is a very sensitive organism easily influenced by the exogenous introduction of many therapeutic preparations, this was not until recently fully appreciated:

> For long the fetus was considered to be little more than an integral part of the mother, requiring little separate consideration from her in respect to the illness from which she might suffer or the drugs she might consume, but the unique individual qualities of the fetus and its dissociation in so many ways from its mother have come to be recognized. The serious fetal abnormalities resulting from a disease as mild as rubella or a drug as generally innocuous as thalidomide exemplify the peculiar vulnerability of the fetus, for it has to be remembered that one of the main grounds for the advocacy of thalidomide in Britain was its safety, the lethal dose for adult or child being very high indeed. (Forfar and Nelson, 1973)

Despite the fact that there was no masculinization of genitalia in any of the 45 females born of the treated pregnancies in this sample and only one of the 71 treated children evidenced any congenital anomaly (one female missing fingers and toes),[3] evidence for psychological or biochemical effects in the absence of morphological change is not unheard of:

> Teratologic effects that are generally, but not categorically, associated with drugs administered during the initial trimester of pregnancy are either nonmorphologic (e.g., induction of fetal enzyme activity by maternally administered drugs; abnormal psychological development in the offspring of women receiving anticonvulsant medication during gestation) or morphologic in nature (e.g., dental dysgenesis produced by tetracycline). (Mirkin, 1973)

Finally, the question of whether these hormones can permeate the placenta, and therefore whether hormones introduced exogenously can directly affect the fetus, is elucidated by a comment from Gillette *et al.* (1973) regarding long-term drug therapy during pregnancy:

> Although the rates at which drugs are transferred across the placenta are obviously important when the drug is given just before delivery or when the drug is rapidly metabolized by the mother, they usually are not very important when the drug is slowly metabolized by the mother or administered repeatedly. Indeed, most drugs used in therapy are usually maintained at rather constant plasma levels for several days and even weeks. Under these conditions, the ratio of fetal plasma level to the maternal plasma level will rise to a constant value, even when the drug is transferred very slowly across the placenta.

This does not rule out the possibility that the placenta or fetus may have altered the original hormone medication into another related compound(s) which then had an effect. Furthermore, most of the mothers in this sample were administered treatment not for just "several days and even weeks" but for at least 4 and as many as 36 weeks.

CONCLUSION

What has been presented here in terms of a relationship between prenatal hormone exposure and personality is only a hypothesis, a tentative beginning to answering an exceedingly complex question for which there are a minimum of data. It has already been demonstrated that hormones introduced during critical periods of early development have far-reaching effects on mammals, fish, and insects. What awaits confirmation is how hormones have the various effects and what all the effects are – and, especially in humans, what the interactions are of postnatal environmental variables with prenatal hormonal influences.

[3] Out the 600 cases reviewed for possible inclusion in this investigation, two other treated children showed congenital defects. They were not included because of the lack of untreated siblings in the family.

ACKNOWLEDGMENTS

The author wishes to thank the Shelton Medical Clinic, the Southern California Fertility Institute, and Dr. Paul Steinberg for generously providing the patient records; Dr. Richard Green and the UCLA School of Medicine, Department of Psychiatry, and Dr. Seymour Feshbach of the Department of Psychology for their generosity in providing technical and clerical support and office space; Dr. Terry Saario of the Ford Foundation, Dr. Suzanne Brainard of the National Institute of Education, and Ms. Zelda Suplee of the Erickson Educational Foundation for their continued help and interest; Carolyn Kaufman, Helen Gordon, and Dana White for their assistance in patient identification, data collection, and coding; Drs. Donald Rubin and John Barone of Educational Testing Service and Dr. Leland van den Daele for statistical device and computer programming; the late Dr. Herbert G. Birch for his encouragement; and most especially Dr. John Money, without whose unstinting support and guidance this study would never have been undertaken.

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