PRENATAL TESTOSTERONE IN MIND

Amniotic Fluid Studies

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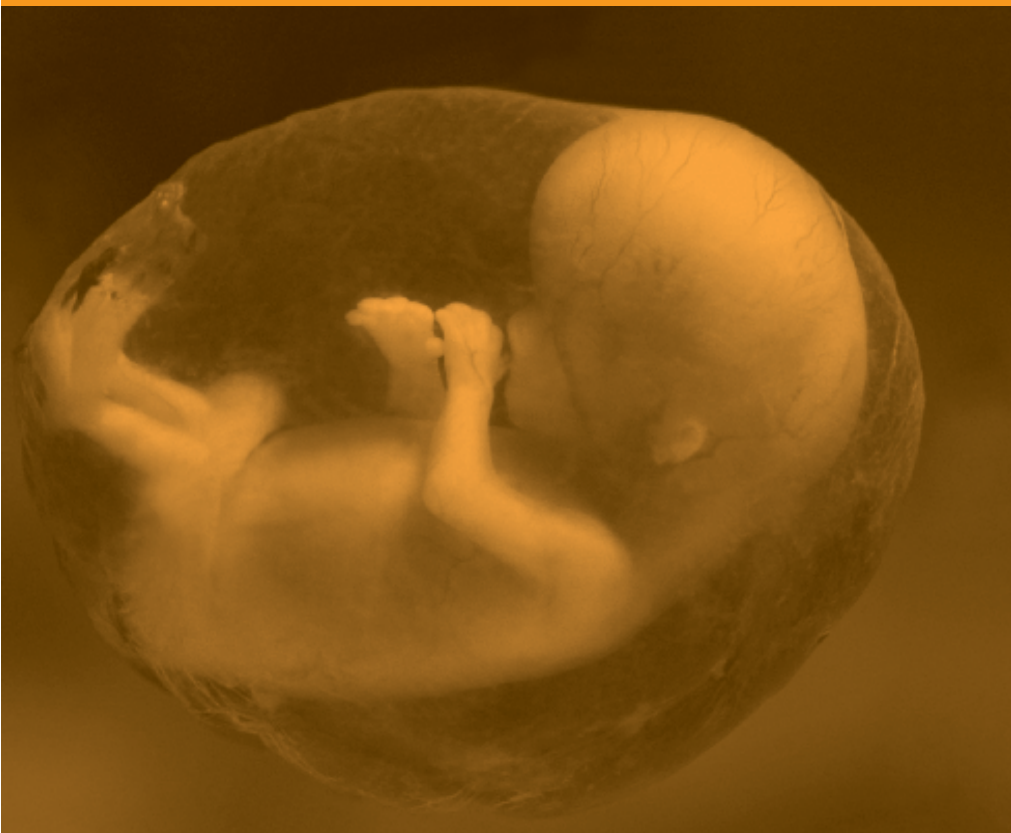
and Rebecca Knickmeyer



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Preface

This is a book about a scientific journey. In our lab, we have been doing something a little bit different. We have not shared it with the outside world until now.

We have written this book primarily for our colleagues in cognitive neuroscience. We do not pretend that it is anything other than technical, specialized, and for the reader with a good background in biology. The general reader may get the gist, but this is a book aimed specifically at our colleagues who have never considered investigating testosterone and who might, after reading about our journey, consider including measures of this vital chemical in their own work. For the general reader, there are other books that are far more accessible; one is *The Essential Difference* (Baron-Cohen 2003).

If you were to visit our lab, you would at first glance think it was just an ordinary set of offices full of graduate students and research associates. But a few minutes later you would in all likelihood notice the enormous deep freezer in Rebecca and Svetlana's office. What lies in the freezer is quite enticing, at least to us. There are thousands of little test tubes, each filled with amniotic fluid from a mother in the Cambridgeshire vicinity. Each test tube represents a child, the vast majority of

who are now happy and healthy 4-year-olds running around Cambridge.

Our research question, which we have pursued doggedly these last 5 years, is this: What, if any, is the relationship between the level of fetal testosterone in the test tube and the child's behavior at the ages of 1, 2, and 4 years?

Each of these test tubes turns out to be—we think—science's best way of getting at a lost past: namely, what was going on chemically when a particular child was in the womb. This isn't about Freudian speculations about the woman on the couch in front of you and whether her early years shaped her adult outcome. Yes, we are interested in the developmental precursors and—dare we say it?—causes of later cognition and behavior. But the test tubes of amniotic fluid mean that we no longer have to be prone to all the potential errors of retrospective speculation or retrospective measurement. We can study development prospectively, from week 16 of gestation, and we can make predictions about the future brain, mind, and behavior of a little fetus.

What could be more exciting to a scientist?

Before you jump on board with us, we should discuss the ethical issues. Amniotic fluid doesn't just fall into scientists' laps. The only reason we scientists even have this opportunity to study neurocognitive development prospectively in this way is that a woman decided, or was advised, to undergo amniocentesis.

In and of itself, amniocentesis is now quite a routine obstetric procedure. Most pregnant women over the age of 35 are encouraged to undergo it, since the risk of having a child with Down's Syndrome increases with age. This is where the ethical issues associated with our research begin. Leaving aside

the ethical decision the woman made in opting to have an "amnio," would she also opt for termination of her pregnancy if markers of Down's Syndrome were identified in the fluid? The fact of the matter is that at the point of "donating" her amniotic fluid to the hospital she was not giving consent for it to be the subject of our research.

"Amnios" are almost invariably stressful. A long needle is needed to draw fluid from the womb, and the expert doctor doing it uses the latest ultrasound technology to ensure that the needle does not touch the fetus. But even so, it is known that a small percentage of pregnancies end in miscarriage after amniocentesis. Thankfully, 98 percent of "amniocentesized" fetuses go on to develop normally and healthily.

The first important ethical step toward using amniotic fluid for scientific study other than that for which it was intended is to obtain fresh consent from each mother. In this book, in addition to explaining the biological interest and the technical issues, and in addition to describing the exciting results obtained from such studies, we detail the ethical issues so that others who are considering similar studies can appreciate how delicate, sensitive, and important this aspect of the work is.

It was crucial to ensure that we would not ask a mother for consent to reanalyze her amniotic fluid (perhaps stored for years) if her pregnancy had sadly ended with a miscarriage or a stillbirth, or if she had opted for termination. To keep a potentially distressing letter from being sent to one of these women inappropriately, Svetlana and Rebecca, the pioneering doctoral students who embarked on the studies described in this book, spent hundreds if not thousands of hours systematically going through the medical records of each and every one

of the women. The strategy was approved by each hospital's Ethics Committee.

Some may object to the term "amniocentesized children." We could not think of another term that so precisely describes who we are studying, and we wanted to put these children at center stage in the play you are about to witness. We hope you will appreciate that these are not children with any medical condition, despite the clinical sound of the term. They are ordinary, happy, healthy, naughty, fun-loving, lovable children who just happen to be a bit different from other children in one respect: their mothers opted for amniocentesis. That may mean the children are not exactly representative of the general population, in that their mothers may be a bit older than average. But from the scientific perspective, we think they are very special. They give us a window—almost like a fossil record—into life in the womb, with which we can compare their current behavior.

Although this book is aimed at our colleagues in cognitive neuroscience, we feel that we are acting as intermediaries between endocrinology and psychology. These two fields are not complete strangers; there is a long tradition of studying the effects of hormones on behavior. The novelty of our work lies in our focus on fetal hormones and their effects on postnatal behavior.

We hope you enjoy the discoveries described in these pages. We still find it remarkable that a few drops of testosterone can affect how much eye contact a toddler makes, or the size of a toddler's vocabulary. These results are counterintuitive. It is widely believed that behaviors such as eye contact and language must be determined by the social environment (parents, sibs, peers) rather than the biological environment. But the

statistics say otherwise. True, the social world makes a contribution, but, as this book shows, so does biology.

Peter Raggatt and Kevin Taylor, biochemists at Addenbrooke's Hospital, guided our investigations and encouraged us to pursue them in the face of what at times seemed like a mountain of practical obstacles. Gerald Hackett, an obstetrician at the Rosie Maternity Hospital, and Steve Smith, head of that hospital, backed our study and helped it through various phases. Jag Ahluwahlia, a neonatologist at the Rosie Maternity Hospital, saw the value of what we were trying to prove and gave helpful advice throughout. German Berrios, chair of the Addenbrooke's Hospital Ethics Committee, helped us see the best way to carry out our study from the perspective of the mothers and children. Ian Goodyer and Joe Herbert, both professors in Cambridge with an interest in what hormones do to our brains, provided us with sound academic support. Melissa Hines in London, a leader in the field of hormones and behavior, provided helpful critiques of our work. Jenny Hannah, our wonderful secretary, gave us support in bringing the book to completion.

We are grateful to the Medical Research Council and the Gatsby Foundation for financial support of the research. In particular, the MRC funded Svetlana's doctoral thesis, from which much of the book is derived. Lastly, and most importantly, our thanks go to the mothers and children who have come back to our lab, year after year, to follow the plot with us.

1
Fetal Testosterone

Endocrine (hormonal) systems are involved in every aspect of pregnancy (including implantation, formation of the placenta, maternal adaptation, and embryonic and fetal development), in birth, and in adaptation to life outside the womb. Hormones have a range of functions involving reproduction, growth, and development, maintenance of the internal environment and the production, use, and storage of energy. Of greatest relevance to this book are the gonadal hormones, which are essential to the sexual differentiation of the fetus. This process includes sexual differentiation of the sex structures, as well as aspects of behavior and cognition (Hadley 2000; Wilson, Foster, Kronenberg, and Larsen 1998; Fuchs and Klopper 1983).

Gonadal Hormones

The gonadal hormones or sex steroids include androgens (e.g., testosterone, dihydrotestosterone), estrogens (e.g., estradiol, estrone, estriol), and progestins (e.g., progesterone). Progesterone is synthesized from cholesterol, and progesterone itself can subsequently be converted to testosterone. And testosterone is a precursor to estradiol and to dihydrotestosterone (Stryer 1995).

Figure 1.1 illustrates the chemical structures of several major gonadal hormones.

Four endocrine glands are capable of synthesizing sex hormones: the adrenals, the testes, the ovaries, and the placenta. The synthesis is the same in all these systems, but the end product of the synthesis depends on the target tissue—for example, the testes secrete testosterone, but the placenta uses it to make estradiol. The process by which testosterone is converted to estradiol is called *aromatization*.

Although estrogen is usually considered to be the female hormone and testosterone the male hormone, both hormones are present in both sexes. The sexes differ in the quantity of each hormone present and in the number of receptors for them (Hess et al. 1997). It is not only the availability of a hormone but also the sensitivity of the target tissue that determines the hormone's biological activity.

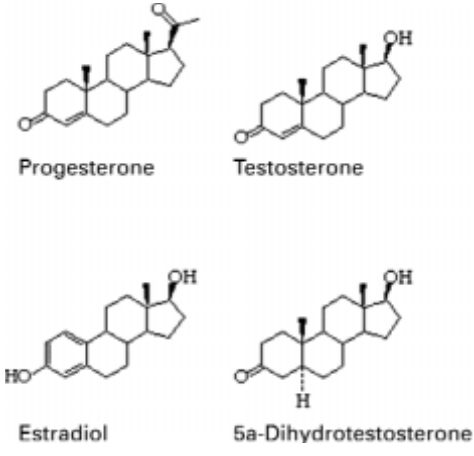

Figure 1.1
Chemical structures of several major gonadal hormones.

Androgens have a number of functions in humans. These include control of gonadotrophin production in the brain, initiation and maintenance of spermatogenesis, promotion of sexual maturity at puberty, control of sex drive, control of sexually dimorphic behavior patterns, and formation of the male phenotype during the sexual differentiation of the fetus. In addition to its involvement in sexual differentiation of the reproductive structures (known as its *androgenic effects*), testosterone is the major hormone responsible for sexual differentiation of such non-reproductive tissues as bone, muscle, kidney, and liver; these effects are called *anabolic* (Bardin and Catterall 1981).

Estrogens are involved in the development of female sexual secondary characteristics, development of the breasts and prevention of bone mineral loss. They have major differentiating effects on the reproductive tract, on the distribution of fat, and on certain bones (including the pelvis), but only minor effects on other organs (Bardin and Catterall 1981). Additionally, there is evidence that estrogens have a neuroprotective role during aging (Witelson 1991). Estrogens are important in the maintenance of pregnancy—for example, they are involved in the support of placental progesterone synthesis, in the increase and maintenance of maternal blood volume, and in the promotion of uterine growth (Repe and Albrecht 1990). There is also some evidence that estrogen has a role in implantation of the fertilized egg. Estrogens can have masculinizing as well as feminizing effects on development.

By week 3 or week 4 of gestation, the placenta is responsible for nearly all estrogen production in pregnancy. Some estrogen is produced by the fetal adrenal gland, which is active from around week 8. The fetal ovary produces little or no estrogen early in pregnancy. No ovarian estrogen synthesis can be detected until late in fetal life. Most of the estrogen is secreted

into the maternal blood, but levels are also high in the fetus and in the amniotic fluid. The role of these high estrogen levels in the fetus is not yet clear. The most abundant estrogen is estriol, which is unique to pregnancy. It is mostly present in an inert form, so the fetus is protected from its potent effects. The mother has a high capacity for rendering estrogen inactive and so does not experience detrimental effects due to high estrogen production by the placenta.

Men normally produce about 100 times more testosterone than estradiol. Most of the estrogen is made from androgens, but the testes also secrete a small amount. Normally insignificant, this can become abnormal in certain medical conditions. Serum concentrations of estradiol are low in males, but they can be higher in semen than in the serum of females. Male reproductive tissues are known to express estrogen receptors, and there is evidence for a physiological role for estradiol in male reproductive function, related to the concentration of semen (Hess et al. 1997).

Progestins can be androgenic or anti-androgenic in their effects, depending on their chemical basis. Their effects are predictable, based on their chemical nature. For example, male-typical behaviors have been observed in females exposed prenatally to androgenic progestins (Collaer and Hines 1995). *Progesterone* is an anti-androgenic or progestational progestin. Progesterone has an essential role in pregnancy maintenance, affecting uterine musculature and inhibiting maternal immune responses to fetal cells.

Another important group of hormones is the *gonadotrophins*, including follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Produced and released by the pituitary gland, these mediate the control of gonad function in both

sexes. In males, FSH and LH are released in a constant, sustained manner and, in females, release is cyclic with a pre-ovulatory surge that leads to ovulation.

Alpha-fetoprotein (AFP), not a steroid hormone, merits discussion at the point because of its potential role in regulating the levels of steroid hormones. It is a globulin produced by the fetal liver and yolk sac during the first and second trimesters of pregnancy, from as early as week 4, and it is often measured during pregnancy (Gitlin, Pericelli, and Gitlin 1972).

Measurement of AFP in amniotic fluid is a reliable indicator of neural-tube defects between weeks 15 and 22 (Wathen, Campbell, Kitau, and Chard 1993). In such cases, maternal AFP levels tend to be high, as AFP leaks from the damaged fetus. In chromosomal disorders, low maternal serum levels could result from impaired fetal kidney function and impaired membrane or placental passage of AFP, rather than reduced fetal production (Van Lith et al. 1991).

AFP can be detected in the fetal brain after 12 weeks, with a peak value in week 20 (Ali, Balapure, Singh, Shukla, and Sahib 1981). Levels decline rapidly after week 24, after which AFP is absent. High levels are said to correspond to the period when critical hypothalamic differentiation is reported to occur in humans (Dörner 1978).

In placental mammals, the fetus is continually exposed to high levels of estrogens from the placenta and the mother. The protective mechanism from these high levels of hormones is well established in rodents. AFP binds to estrogen, but not to testosterone. However, AFP does not bind to estrogen in humans (MacLusky and Naftolin 1981). The mechanism by which the human fetus is protected from high levels of estrogens is not fully established.

The Placenta

The fetal hormone environment is dependent on a functioning placenta (Chara 1982) that regulates the exchange of molecules between the fetus and the mother. This means that the fetal environment is largely independent of maternal hormones, because the placenta is impermeable to most hormones. The placenta synthesizes estrogens, progesterone, polypeptide hormones, neuropeptides, and growth factors. The placenta has a very strong aromatizing enzyme system, and androgens tend to get converted to estrogen by it. This means that very little androgen is transmitted by the placenta.

Becoming Male or Staying Female: Sexual Differentiation of the Fetus

Gonadal hormones are responsible for differentiation of the male and female phenotypes in the developing human fetus (MacLusky and Naftolin 1981; Fuchs and Klopper 1983; Wilson et al. 1998; Kimura 1999), although direct genetic influences on sexual differentiation of the brain are increasingly recognized (Devries 2002, Arnold 1996). There are five major stages in normal sexual development.

The *genetic sex* is determined at the moment of conception by the presence of an X (female) or a Y (male) chromosome in the fertilizing sperm cell. The karyotype of the normal female is 46 XX; that of the normal male is 46 XY. Each is made up of 44 autosomes and 2 sex chromosomes. The male can be described as heterogametic, the female as homogametic. There are very few differences between the genes of males and females, except for the Y chromosome in the male (Bardin and Catterall 1981).

The genetic sex determines whether testes or ovaries develop (i.e. *gonadal sex*). Up until week 6, genetically male and genetically female fetuses are undifferentiated—that is, there is no difference between them with respect to their reproductive structures. During week 6, the Sry gene on the Y chromosome initiates testicular differentiation in the male; this is thought to be the major function of the Y chromosome. The Leydig cells of the testis are capable of synthesizing testosterone by the end of week 8. Further development of the Leydig cells means that testosterone secretion is high between weeks 10 and 20. Fetal synthesis of testosterone is probably controlled by hcG (human chorionic gonadotrophin) and LH from the fetal pituitary. In addition, males are exposed to fetal testosterone from the fetal adrenals.

In the female, differentiation of the ovaries begins around week 7. The fetal ovary may produce a small amount of estrogen (Smail, Reyes, Winter, and Faiman 1981). The female fetus is also exposed to low levels of androgens. A small proportion may come from the fetal adrenals, and some comes from the maternal adrenals, ovaries, and fat (Geschwind and Galaburda 1985b; Martin 1985).

The secretions of the gonads thus formed determine the *phenotypic sex*. If male sex hormones and the appropriate receptors are present, the male phenotype will develop; if sufficient male sex hormones or functioning receptors are not present (i.e., in females), the female phenotype will develop (Jost 1961; Jost 1972; Donahoe, Cate, and MacLaughlin 1987; George and Wilson 1992). The internal genitalia of both sexes are derived from the Wolffian (male) and Müllerian (female) ducts, which co-exist in the undifferentiated developing embryo. In the male, between weeks 8 and 14, the Wolffian ducts, stimulated by

testosterone, develop into the male internal structures. The Müllerian ducts regress, thus preventing the formation of female internal structures. Regression of the Müllerian ducts is caused by anti-Müllerian hormone or Müllerian regression factor (secreted by the Sertoli cells of the testes). The formation of the male external genitalia is stimulated by dihydrotestosterone, which is formed from testosterone by 5-α-reductase. In the female, the absence of testosterone causes the Wolffian ducts to atrophy. The absence of anti-Müllerian hormone allows the Müllerian ducts to become the female internal structures. Similarly, the absence of male sex hormones allows female external genitalia to develop, rather than male structures.

Neuronal sex (which refers to male-type or female-type gonadotrophin secretion, sexual orientation, and gender role behavior) and *gender identity* (Dörner et al. 1987) are shaped to a large extent by prenatal factors.

In summary, masculinization requires the action of testicular hormones. The default mammalian sex is female, and in the absence of very high levels of male sex hormones female structures will develop. It has been assumed that no special hormonal environment is required for the formation of the female phenotype. That traditional model is now being replaced by a more complex one which recognizes that small amounts of ovarian hormones may be required for active feminization of the female brain (Beyer 1999). Still, many stages must be completed successfully if the male phenotype is to develop, and these stages rely to a large extent on the existence of the right hormonal environment. This implies that there are a number of stages at which the normal development of the male could be disrupted.

Not all animals have female as the default sex. In birds, for example, the default homogametic sex is male, and differenti-

ation of the female depends on exposure to ovarian hormones. In mammals, fetuses are exposed to high levels of female hormones from the mother, so it is adaptive for the default sex to be female. In egg-laying species this does not apply, so having one sex as the default sex over the other does not necessarily confer the same advantages as in mammals (Hadley 2000). It is interesting to note that feminization of the brain in mammals by ovarian estrogen is thought to occur at a later period than masculinization (in female rats this may extend from the late neonatal to the pubertal period and perhaps even into adulthood) (Fitch 2002, p. 365). This would mean that ovarian-estrogen-mediated feminization takes place after the individual is free from the maternal-hormonal environment of the womb.

Organizational versus Activational Effects, and Sensitive Periods

Sex hormones have two different types of effect on tissue: organizational and activational (Goy and McEwen 1980). Organizational effects are permanent and happen early in development, usually during a sensitive period. Activational effects happen later in development and are superimposed on the early organizational effects. The later hormonal actions are necessary if the tissue or organ in question is to perform its function. For example, the tissues of the genetic male are organized prenatally for male adult reproductive behavior. However, the male will not display such behavior unless adequate sex hormones are produced at puberty. Although the dichotomy between organizational and activational effects is useful for understanding hormonal effects, it cannot always be rigidly applied (Arnold and Breedlove 1985). When studying

the organizational effects of hormones on the developing fetus, it is important to remember that later activational effects may be essential to the function in question. For estrogen the distinction is particularly problematic, as estrogen appears to exert "organizational" effects for a very long period of time.

Both adult and fetal studies can be subject to the same criticism: the relationship between the time of measurement and the sensitive period for development is unknown. Sensitive (or critical) periods are hypothetical windows of time in which a tissue can be modified. Environmental disruptions during development can have devastating effects. A substance that causes damage curing a critical period may have no effect at all when development is complete. It is therefore adaptive to restrict development to specific, limited time periods. This means, for example, that circulating sex hormones necessary for adult sexual functioning do not cause unwanted alterations to tissues, even though the same hormones might have been essential to the development of those tissues. Different behaviors can have different sensitive periods for development. For example, androgen exposure early or late in gestation has differential effects on male typical juvenile behaviors in the female rhesus macaque (Goy, Bercovitch, and McBrair 1988).

Postnatal Hormone Surges

Neonatal

After the prenatal surge in testosterone production, there are two further testosterone surges in the human male. These occur neonatally and at puberty. Although the function of the neonatal surge is not fully understood in humans, it is likely to be related to the preparation of tissue for subsequent androgen

mediated growth. In monkeys, disruption of the neonatal surge is known to lead to disrupted testicular function at puberty (Mann, Gould, and Collins 1989). As males may experience a testosterone surge at this time and females do not experience such a surge, the same amount of subsequent testosterone exposure will have very different effects on each sex (MacLusky and Naftolin 1981). Females experience a postnatal surge in estradiol production, which is thought to come from the ovaries (Bidlingmaier, Strom, Dorr, Eisenmenger, and Knorr 1987). Levels remain high for the first year of life, peaking around month 3 or 4. Median levels are equivalent to those in the second stage of puberty (Bidlingmaier, Versmold, and Knorr 1974). The postnatal surges in both sexes are stimulated by surges in gonadotrophin levels (Bidlingmaier et al. 1987).

Pubertal

Sexual differentiation is not complete until puberty, when secondary sexual characteristics develop and fertility is attained. The development of the gonads can be viewed as a continuum from the fetal stage to puberty, with reproduction as the ultimate goal.

Factors That Influence Testosterone Levels

The factors that influence testosterone levels, both prenatally and postnatally, include stress, alcohol use, smoking, and the spacing of births (Dorner et al. 1987).

Prenatal stress in male rats demasculinizes and feminizes adult sexual behavior (Ward 1977), and testosterone levels in newborn rats are reduced in stressed animals relative to nonstressed controls (Stahl, Gotz, Poppe, Amendt, and Dorner

1978). Human homosexual males report more stressors (such as bereavement) during their mother's pregnancy than controls (Dorner, Schenk, Schmiedel, and Ahrens 1983). In females, there is some evidence that prenatal stress is associated with male typical gender role and sexual behavior.

Testosterone and estradiol are also significantly decreased in alcohol users (Westney et al. 1991). Serum testosterone levels are positively correlated to smoking in mothers during pregnancy, and also in their adult daughters. Daughters' smoking during adolescence is influenced by mothers' smoking during pregnancy and by maternal testosterone levels during pregnancy. In addition, maternal testosterone during pregnancy influences daughters' testosterone level, so this could be one mechanism whereby testosterone levels are transmitted from one generation to the next (Kandel and Udry 1999).

Hormone levels during a pregnancy are also influenced by how recently the mother has had a child. First-borns of both sexes have higher estrogen and progesterone levels, and male first-borns have higher testosterone than later-borns, when these are measured in umbilical-cord blood. This is not due to maternal age, length of labor, or birth weight. Close spacing of childbirths (i.e., less than 4 years) results in lower-than-normal hormone levels. The reduction in hormone levels is greater when the fetuses are male. After 4 years, levels are at first-born levels or higher (Maccoby, Doering, Jacklin, and Kraemer 1979).

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