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Summary report

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Technical consultation on hormonal contraceptive use during lactation and effects on the newborn

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Photo: WHO - P. Virot

Contents

RHR
Department of Reproductive Health and Research

Abbreviations and acronyms

BPA	bisphenol A
CHC	combined hormonal contraceptive
COC	combined oral contraceptive
CYP	cytochrome P450
DES	diethylstilbestrol
DMPA	depot medroxyprogesterone acetate
IUD	intrauterine device
NET-EN	norethisterone enantate
POC	progestogen-only contraceptive
RHR	Department of Reproductive Health and Research
RU486	mifepristone
WHO	World Health Organization

Technical consultation on hormonal contraceptive use during lactation and effects on the newborn.

Introduction

The Department of Reproductive Health and Research (RHR) of the World Health Organization (WHO) produces evidence-based guidance on contraceptive use, which includes the *Medical Eligibility Criteria for Contraceptive Use, Third Edition, 2004* and *Selected Practice Recommendations for Contraceptive Use, Second Edition, 2004*. The *Medical Eligibility Criteria for Contraceptive Use* provides recommendations on the use of various contraceptive methods by women and men with specific characteristics or with known pre-existing medical conditions. The *Selected Practice Recommendations for Contraceptive Use* provides guidance on how to use contraceptive methods safely and effectively once they are deemed medically appropriate. The Department carefully monitors the publication of new research evidence and, together with the Guidelines Steering Group, keeps these guidelines up to date with the state of knowledge in the field.

Since these guidelines were published, the Department updated systematic reviews with new evidence on hormonal contraception use among breastfeeding women, and the effects of such use on the newborn. These systematic reviews were initially reviewed by experts in family planning, and subsequently discussed at the meeting of an Expert Working Group held at WHO Headquarters, Geneva, Switzerland, 31 March to 4 April 2008. In light of the presented evidence, this Expert Working Group determined that WHO should reconsider their recommendations on use of progestogen-only contraception by breastfeeding women during the first six weeks postpartum, but that additional expertise was necessary. Based on this appraisal, the WHO Secretariat and the Guidelines Steering Group determined that it was necessary to convene a technical consultation to evaluate thoroughly the evidence surrounding the use of both combined (estrogen and progestogen) hormonal contraceptives and progestogen-only contraceptives by breastfeeding women during the first six weeks postpartum.

A technical consultation evaluating the effect of hormonal contraception use in the first six weeks postpartum by lactating women on their newborn children was convened at WHO Headquarters, Geneva, 22 October 2008. The consultation brought together the Guidelines Steering Group, other experts on hormonal contraception, experts on steroidal hormones and experts in neonatal development and care, to evaluate all available scientific data in this area. All participants in the meeting were asked to declare any conflict of interest. One expert declared a conflict of interest relevant to the subject matter[1] and was not asked to withdraw from recommendation formulation. Along with the presentation of updated systematic reviews of direct human evidence on the use of combined hormonal contraception and progestogen-only contraception during lactation and effects on the neonate, the participants were presented with data on the ability of neonates to metabolize exogenous substances, and the effect of endogenous estrogen and progesterone on brain development in animal models. This report summarizes the material presented to participants during the consultation.

Following these presentations, participants reviewed current WHO recommendations on the use of hormonal contraceptives during lactation, taking into consideration any potential effects on neonatal development. These recommendations appear on the WHO website (http://www.who.int/reproductivehealth/publications/family_planning/WHO_RHR_09_13/en/index.html) and at the end of this report.

[1] Dr Glasier works at a clinic that receives research support from four companies that manufacture various contraceptive products.

Review of evidence

Hormonal contraceptive use during breastfeeding and its effects on the neonate

Dr Nathalie Kapp (WHO Secretariat) presented the results of two systematic reviews conducted by RHR to assess the effect on breastfed infants and children of combined hormonal contraceptive (CHC) use and progestogen-only contraceptive (POC) use by their mothers during the first six weeks postpartum. These reviews focused on clinical outcomes of breastfeeding, such as duration of breastfeeding, use of supplementation and weaning, as well as clinical outcomes in the breastfed child, such as growth and development.

As this consultation focused on the development of the breastfed newborn exposed to maternal hormonal contraceptives, only those studies assessing neonatal outcomes were considered. A Cochrane review was previously conducted to determine the effect of hormonal contraceptives on lactational parameters such as milk composition, volume, or amount of hormones transferred to breast milk. It included seven reports of five different randomized trials, and concluded that the existing randomized controlled trials do not provide sufficient evidence to make recommendations regarding hormonal contraceptive use in lactating women *(1)*.

Use of combined hormonal contraceptives and breastfeeding

The MEDLINE and Cochrane databases were searched for all relevant articles published from database inception until August 2008. Outcome measures were growth, development and health of infants whose mothers began use of CHC methods at no more than six weeks postpartum. Studies reporting solely on milk composition, amount of hormones transferred to milk, or milk quantity were not included. Four studies met inclusion criteria: three randomized or partially randomized controlled trials *(2–5)* and one Cochrane systematic review *(1)*. These studies, as well as three additional studies where contraceptive use was begun around six weeks postpartum *(6–8)*, were presented.

Data were limited by multiple factors: in only a few studies was contraception initiated during the neonatal period (defined as the first 28 days postpartum); the follow-up of children exposed to contraceptive hormones through breast milk was short and focused on height and weight as outcome measures in children, to the exclusion of other, more sensitive developmental measures; many studies had small numbers of participants, and generalizability of findings may be limited as many studies restricted enrolment to multiparous women with a history of successful breastfeeding. Furthermore, studies were limited to combined oral contraception (COC), to the exclusion of other combined hormonal methods of contraception.

The earliest randomized controlled trial compared 212 healthy infants of women receiving COCs (norethisterone 1 mg/mestranol 0.05 mg daily) with 218 healthy infants of women receiving placebo, initiated 24 hours postpartum *(2)*. There were no significant differences in infant weight by day eight postpartum, although more infants in the COC group required supplemental feeding (12.3% compared with 3.4%, $p<0.05$). A later randomized controlled trial compared the effect of a daily combined pill containing norethisterone1 mg/ mestranol 0.08 mg with placebo, initiated at two weeks postpartum *(3)*. Infant weight gain was lower in the 24 infants in the COC group when compared with the 23 infants in the placebo group at four and five weeks postpartum, although no differences were seen at three months; there were no differences in infant health. In a partially randomized Chilean study, the average weight of exclusively breast-fed infants whose mothers began daily COCs containing levonorgestrel 150 µg/ ethinylestradiol 0.03 mg at 30–35 days postpartum

(*n*=103) was lower between days 61 and 183, and at day 366 of life, when compared with the placebo group (*n*=188), but not when compared with infants of mothers who used an intrauterine device (*n*=118) *(4, 5)*. Women who supplemented feeding were excluded from analysis; a significantly higher proportion of women in the COC group used supplementation (exclusively breastfeeding at 91 days postpartum: COC group=81%, placebo group=92%, IUD group=92%, $p<0.05$). There were no differences in infant weights measured at other time points, or in overall health, between the groups.

In three studies included in the presentation, COCs were initiated around six weeks postpartum. These include a multicentre study comparing the infants of women using COCs (levonorgestrel 150 µg/ethinylestradiol 0.03 mg daily, *n*=86), the injectable progestogen contraceptive depot medroxyprogesterone acetate (DMPA 150 mg, *n*=59), progestogen-only pills (norgestrel 0.075 mg daily, *n*=85), and nonhormonal methods (*n*=111) *(6)*. No differences between infant weight, growth, or episodes of illness were observed between groups after 24 weeks of follow-up. A Swedish cohort study followed infants whose mothers initiated use of COCs (progestogen component not stated/ethinylestradiol 0.05 mg daily, *n*=48) at eight weeks postpartum, and compared them with infants whose mothers received nonhormonal methods of contraception (*n*=48) *(7)*. Over eight years of follow-up, infants in the two groups demonstrated no differences in development, episodes of illness, or school performance. Finally, a Chilean cohort study examined weight gain in infants whose mothers initiated COC use (levonorgestrel 15 µg/ethinylestradiol 0.03 mg daily, *n*=59) at 90–95 days postpartum, compared with nonhormonal methods (*n*=82) *(8)*. Despite lower weight gain noted at four months in the COC group, no differences were seen at any other time points during the year-long follow-up period.

In summary, the evidence regarding the use of combined hormonal contraception during lactation is limited and largely of poor methodological quality. Studies fail to demonstrate a significant difference in infant outcomes, with one exception which demonstrated lower infant weights at multiple time points over one year. No studies demonstrated adverse health outcomes in infants such as poor health or poor school performance.

Use of progestogen-only contraceptives and breastfeeding

A second systematic review investigated the effects of POC use during breastfeeding by searching the MEDLINE, LILACS and Cochrane databases for all relevant articles published from database inception until August 2008. Outcome measures of interest were infant growth, development, and health of breastfed babies whose mothers initiated POCs (oral, injectable, implantable or hormonal-releasing IUDs) at less than six weeks postpartum. Studies reporting solely on breast milk composition, hormonal content or quantity were not included. A total of 13 studies were presented: 2 controlled or partially controlled trials *(9, 10)*, and 11 observational studies *(11–21)*. Overall, the body of evidence was limited by the small number of studies where contraceptive use was initiated during the neonatal period; the short duration of child follow-up in most studies; and emphasis on infant growth as an outcome measure, to the exclusion of other, more sensitive measures of development. Finally, studies included a wide range of progesterone and progestogen-containing contraceptives, results from which may not be applicable to other formulations.

In the earliest published study included in the review, children from a cohort of Egyptian women initiating either norethisterone enantate (NET-EN 200 mg, *n*=125), DMPA (150 mg, *n*=106), or a nonhormonal IUD (*n*=100) at either 7 or 42 days postpartum were followed for 18 months *(11)*. Infant weight gain per month was noted to

be higher in the groups taking hormonal contraceptives than in controls, and no physical, mental, or radiological abnormalities were reported over the time frame of the study. A retrospective cohort study compared breastfed children whose mothers initiated DMPA (150 mg) between four and eight weeks postpartum (*n*=173) to children not exposed (*n*=198) *(12)*. There were no differences in overall health, psychomotor development, physical examination, achievement of developmental milestones, or height at three to six years of age between the two groups. Child weight, when adjusted for confounders, did not differ between groups.

Two studies evaluated effects of maternal implantable progesterone pellet use on infants. One cohort study found no differences in infant growth, weight or morbidity at six months between those initiating pellets (*n*=277), copper-releasing IUD (*n*=246), or placebo (*n*=130) on postpartum day 30 or 60 *(13)*. A partially controlled randomized trial also compared pellets (*n*=84) to copper-releasing IUD (*n*=125) and placebo (*n*=130), but with initiation of method or placebo between postpartum day 30 and 35 *(9)*. In this study, infants followed for 12 months showed no differences in weight, growth, or health outcomes.

Four studies compared progestogen-releasing implants to nonhormonal methods initiated between four and nine weeks postpartum. The first of these compared infants whose mothers initiated the levonorgesterol implant Norplant (*n*=50) between four and six weeks postpartum to those using the copper-releasing IUD (*n*=50) or barrier methods (*n*=50). No differences in infant weight were found between the groups after six months of follow-up *(14)*. A second cohort study examined infants whose mothers used the nomegestrol implant Uniplant (*n*=120) and those exposed to the copper-releasing IUD (*n*=120) *(15)*. Contraceptives were initiated between five and nine weeks postpartum; at 12 months there were no differences in growth between the two groups *(15)*. One small study found no differences in maternal or infant immunoglobulin levels measured six months postpartum between breastfeeding mothers who had initiated Norplant (*n*=10) between four and six weeks postpartum, and those who had not (*n*=10) *(16)*. Another cohort study compared follicle stimulating hormone, luteinizing hormone and testosterone levels in male infants whose mothers initiated either levonorgestrel pills (0.03 mg daily, *n*=9), Norplant (*n*=10), or no method (*n*=10) four weeks after delivery *(17)*. No differences in endogenous hormone levels were found up to 15 weeks postpartum.

A cohort study compared infants of women initiating levonorgestrel pills (0.03 mg daily, *n*=150) at one week postpartum to those using copper-releasing IUD (*n*=150), finding no difference in growth between the two groups during the nine month follow-up period *(18)*. In one study comparing desogestrel pills (75 µg daily, *n*=42) initiated between 28 and 56 days postpartum, and copper-releasing IUD (*n*=41), desogestrel use was associated with temporary breast enlargement in two infants *(19)*. No clinically relevant effects were present after two and a half years of follow-up.

Finally, two studies comparing the progesterone-releasing vaginal ring (total *n*=1090), initiated between four and nine weeks postpartum, to the copper-releasing IUD (total *n*=996), showed no difference in infant growth through 12 months of age *(20, 21)*. A randomized controlled trial compared the growth and health of the infants of mothers assigned to two different doses of a levonorgestrel-releasing IUD (10 µg/day, *n*=30; 30 µg/day, *n*=40) to 40 women assigned to the copper-releasing IUD *(10)*. No differences in infant height or weight were seen up to 12 months of age, and no differences were observed between groups in age at first tooth, age at first ambulation, number of respiratory tract infections, or blood chemistries.

In summary, studies examining the use of progestogen-only contraception prior to or around six weeks postpartum have shown no adverse effects on measures of infant growth, development, or health. However, the methodologies employed in these studies to assess the effect of drug exposure during the neonatal and newborn period have been less than optimal; most studies instituted POCs towards the end or after the first six weeks postpartum, had relatively short follow up periods, and assessed endpoints that would not have detected longer-term or behavioural effects of exposure on children.

Neonatal metabolism of exogenous substances

Dr Betty Kalikstad (University of Oslo, Norway), presented a review of neonatal metabolism of drugs and other exogenous substances.

Transfer of contraceptive hormones to breast milk and the neonate

Two studies have measured the amount of ethinylestradiol, an estrogen commonly used in CHCs, in breast milk. In one study, four fully breastfeeding women were given a COC containing megestrol acetate 4 mg/ethinylestradiol 50 µg daily beginning at two months postpartum. Ethinylestradiol was undetectable in the participants' breastmilk (<50 ng/l) after 10 days of therapy. In the same study, a second group of four women who were 6–18 months postpartum were given a single oral dose of ethinylestradiol 500 µg. Peak levels in breast milk ranged from 170 to 300 ng/l. Based on these data, authors calculated the dose received by fully breastfeeding infants to be 0.02% of the dose given to their mothers; for women taking 50 µg of ethinylestradiol daily, this translates to 10 ng daily *(22)*. In a second study, milk was collected and pooled from two groups of women taking ethinylestradiol 100 µg three times daily. Pooled milk was evaluated for estrogenic activity and compared with pooled milk from women who were not taking steroids. No increase in estrogenic activity was detected in women taking ethinylestradiol *(23)*. In neither study were the serum levels of contraceptive hormones measured in infants.

In four studies levonorgestrel levels were measured in maternal breast milk following treatment with oral levonorgestrel, either alone or in combination with estrogens. All studies were small, ranging from 2 to 15 participants; treatment was initiated at different times postpartum; and varying dosing and measurement strategies were used. Levonorgestrel levels in breast milk of women receiving 30 µg of levonorgestrel daily were reported as undetectable to 0.05 µg/l *(24–26)*, women who received 150 µg of levonorgestrel daily had peak levels of 0.34–to 0.54 µg/l and average levels of 0.18 µg/l *(26, 27)*, and women who received 250 µg of levonorgestrel daily had peak levels of 0.51–1.05 µg/l and average levels of 0.64 µg/l *(24 ,26)*.

Two additional studies examined levels of levonorgestrel in breast milk in women using Norplant. In one study, 100 women who received Norplant at an average of 55 days postpartum were compared with 100 women who received a non-hormonal IUD postpartum. Milk levonorgestrel levels increased in the Norplant group, reaching a peak of 0.163 µg/l on days 16–22 post-insertion, after which they declined *(28)*. Another study compared breast milk hormone levels in 14 women who received Norplant, 14 women who received an IUD which released 20 µg of levonorgestrel daily, and 10 women who received levonorgestrel 30 µg orally daily for 28 days. Contraceptive methods were initiated between four and six weeks postpartum. The average level of levonorgestrel in the Norplant users was 0.067 µg/l, in IUD users was 0.046 µg/l, and in pill users (reported above) was 0.05 µg/l *(25)*.

In three studies, levels of levonorgestrel have been measured in the blood of breastfed infants. In one, infant serum levels were measured in 10 fully

breastfeeding women who received a single 30 µg dose of levonorgestrel, and 15 women who received a single dose of 250 µg. Women were eight weeks postpartum. Infant serum levels taken 1.5–2 hours after breastfeeding, and four hours after maternal dosing, were 0.019 µg/l in the 30 µg group, and 0.078 µg/l in the 250 µg group *(24)*. In another study, two, eight week-old infants whose mothers were taking a COC containing 250 µg of levonorgestrel/50 µg ethinylestradiol had plasma levonorgestrel levels measured five hours after the maternal dose, and two hours after nursing. Levels were 0.058 and 0.115 µg/l in the two infants, respectively. A third infant, whose mother took 30 µg levonorgestrel tablets daily, had undetectable plasma levels of hormone *(26)*. Authors concluded that the infants were able to metabolize levonorgestrel. One additional study measured maternal and infant serum levels of levonorgestrel in 43 women initiating Norplant between 30 and 40 days postpartum *(29)*. Each maternal-infant pair gave one venous blood sample at some point during the first year postpartum; one pair gave two samples. Ten samples were taken during the first postpartum month, 3 during the third, 12 during the sixth, 8 during the ninth and 11 during the 12th. Infant serum levonorgestrel concentrations ranged from 1.5 µg/l to 4.2 µg/l, and averaged 9.9% (range 4.9–12.6%) of simultaneous maternal serum levels, although the correlation between maternal and infant levels was low (correlation coefficient r=0.27).

Two studies document levels of DMPA in breast milk. In one of these studies, seven women were administered 150 mg of DMPA intramuscularly one week after delivery. Peak levels in breast milk occurred 8–28 days after injection, and ranged from 1.3 to 2.3 µg/l *(27)*. In the second study, women received 150 mg of DMPA intramuscularly at 6–7 weeks postpartum *(30)*. Peak levels of 7.5 µg/l were detected about 1 week after injection, falling to about 0.5 µg/l by 12 weeks. The authors estimated that fully breastfed infants would receive a dose of medroxyprogesterone acetate between 1 and 13 µg/day 1 week following injection, and as much as 1 µg/day at 12 weeks. In one study, infant exposure to DMPA was measured, not through serum hormone levels, but by examining urine for metabolites. In this study, the urine of 13 breastfed male infants of women who received one injection of 150 mg of DMPA at 6–18 weeks postpartum was examined for medroxyprogesterone acetate or its metabolites; none was detected *(31)*.

In summary, although there are few studies and limited numbers of participants, the amount of ethinylestradiol present in breast milk reported is low, typically 1% or less of the maternal dose *(32)*. Similarly, the progestogen dose present in breast milk is estimated to be approximately 0.1% of the oral maternal dose, although peak levels of medroxyprogesterone acetate present in breast milk are higher. However, infant absorption, distribution, and metabolism, which have not been well studied, may further affect the effective dose.

Drug metabolism in infants

As in adults, multiple mechanisms of drug metabolism exist in infants and children. However these systems are continually evolving as newborns mature. In addition, these dynamic systems may be adversely affected by multiple factors, most commonly prematurity or illness. The essential elements of pharmacology – absorption, distribution, metabolism and elimination – remain poorly characterized in children, particularly in neonates. Thus, it is difficult to understand the metabolism of a specific substrate, in this case the synthetic hormones used in contraceptives and excreted in breast milk. General information about these processes, as it is currently understood, was presented.

Synthetic steroid contraceptive hormones excreted in breast milk are ingested orally by infants, and are absorbed via the gastrointestinal tract. Changes in intraluminal pH of different segments of the gastrointestinal tract, gastric emptying times, and

intestinal motility associated with development during the neonatal period affect the absorption of those substances consumed by newborns. There is a dearth of data directly evaluating the effect of these changes in infants. However the few available studies suggest that these absorptive processes are mature by four months of age *(33)*. Due to the immaturity of this system, the rate of gastrointestinal absorption of drugs is slower in neonates compared with older children or adults, leading to lower plasma drug levels in very young infants. In addition, developmental differences in the activity of the drug metabolizing enzymes within the gastrointestinal tract, such as cytochrome P450 (CYP) enzymes and glutathione *S*-transferase, drug transport proteins, and changes in gut bacterial flora as the newborn matures, likely affect the absorption and distribution of orally consumed drugs.

As in adults, drug metabolism in children is largely carried out by Phase I and Phase II enzyme systems localized in the liver. Phase I enzymes, composed of the CYP system, are responsible for oxidation, reduction and hydrolysis, while Phase II enzymes further conjugate partially metabolized drugs, rendering them water soluble and excretable. In adults, progesterone is metabolized in the liver by the Phase I enzyme cytochrome P450 2C19 (CYP2C19) to pregnanediols and pregnanolones. Subsequent conjugation by Phase II proteins converts these substances to glucuronide and sulfate metabolites, which are largely excreted in the bile. The expression of the CYP enzymes in newborns changes markedly with development. CYP3A7 is the predominant CYP isoform expressed in the fetal liver. Its levels decline approximately one week before birth, only to peak again shortly after parturition. Levels subsequently decline to almost undetectable, as adult CYP isoform levels, such as CYP3A4, rise *(34)*. Multiple CYP isoforms (CYP2E1, CYP3A4, CYP2C, and CYP2C19) appear within the first days to months of life *(35–37)* in distinct patterns that are not well understood. Even less is known about the development of Phase II enzymes, although available data indicate that they, too, have individual maturational profiles *(38)*.

Although little is known about drug metabolism in infants, it is clear that some metabolic capacity exists at birth, and that metabolic processes mature as newborns grow and develop. The mechanisms of absorption and metabolism of contraceptive hormones in infants less than six weeks of age have not been delineated. Few studies have examined serum hormone levels or presence of metabolites in the breastfed infants of women using contraceptives, and although reported levels are low, it is unknown when and how effectively the maturing neonatal metabolic systems are able to process these compounds. Finally, no data exist documenting the amount of these compounds available to the infant brain.

Effects of estrogenic steroids on the developing brain

A review of the effects of estrogens in the developing brain was provided by Dr Jaclyn Schwarz (University of Maryland, USA). Dr Schwarz attempted to answer three questions: (1) is the human neonatal brain sensitive to estradiol; (2) what are the effects of estrogen on the developing brain; and (3) is there any evidence that estradiol or its conjugates impairs the developing brain? Given the lack of evidence elucidating the effects of estrogenic steroids in the human brain, data presented focused on animal models.

Is the human neonatal brain sensitive to estradiol?

Rat models provide the preponderance of evidence regarding effects of estradiol on the developing brain. In these models, steroidal hormones play a critical role in the sexual differentiation of the brain. Several days prior to parturition, the testes of male rats begin to secrete significant quantities of testosterone. This testosterone induces the formation of male secondary sexual characteristics,

and plays a necessary role in the sexual differentiation of the developing rat brain. Testicular testosterone is converted to estradiol within the brain by aromatase enzymes present in the neurons themselves *(39, 40)*. Locally produced estradiol is responsible for organizing sexual differentiation in the brain, and aromatase is expressed in those regions of the rat brain significant for this differentiation. For brain masculinization to occur, exposure of the male rat brain to high perinatal levels of testosterone, with subsequent local conversion to estradiol in these sex specific areas, must take place during a limited "critical period" which lasts only a few days after birth. While this series of events has not been elucidated in humans, there is evidence to suggest that similar processes occur. Testosterone levels transiently rise in human males soon after birth, reaching peak levels not observed again until puberty and adulthood. Localization of aromatase enzyme to neurons is preserved across species, including humans and non-human primates (*41, 42)*, and aromatase activity has been observed in the developing primate brain *(43)*. Estrogen receptors, localized to sexually dimorphic brain regions in rats, have been observed in human prefrontal cortex, cerebellum, and hippocampus *(44–46)*. Presence of these receptors indicates that exposure to estrogens will have an effect on the neonatal human brain, although that effect has not been described. Finally, a restricted period during which sexual differentiation of the brain can occur, identified as the "critical period" in rats, has also been identified in multiple animal species, suggesting a process likely conserved in humans as well *(47–50)*. While the "critical period" lasts only a few days in rats, it lasts several months in primates. The duration of such a period in humans is unknown.

What are the effects of estrogen on the developing brain?

In rodent models, effects of estradiol on the developing brain are best observed and most clearly characterized in those regions responsible for sexual differentiation. Four important processes in brain development have been described: cell genesis, apoptosis, cell differentiation, and formation of synaptic connections. Estradiol induces each of these processes, often via strikingly different mechanisms and in distinct regions of the brain. In particular, estradiol effects have been described in those regions related to sexual and reproductive behaviour, including the hippocampus, the sexually dimorphic nucleus of the pre-optic area, the ventromedial nucleus of the mediobasal hypothalamus, the arcuate nucleus, and others *(51–53)*. Although the individual mechanisms are unique, and lead to both micro and macro changes in the rodent brain, the sum total of these effects is the induction of two distinct processes responsible for sexual differentiation of the male rat brain during the "critical period" described above. Not only are the male rat neural circuits that allow for adult masculine behaviour induced by estradiol (masculinization), but also the capacity to express female sexual behaviour is concomitantly eliminated (defeminization). These estradiol induced processes result in the phenotypic male brain in the rat. In contrast, feminization occurs in the absence of critical levels of neuronal estradiol, and results in female-typical behaviour *(45)*.

Is there any evidence that estradiol and its conjugates impair the developing brain?

Few synthetic estrogens have been studied in the developing brain. Of those estrogens utilized in contraceptives, only ethinylestradiol has been formally examined. Two studies document decreases in several steroidogenic proteins, including aromatase, in salmon embryos and juvenile salmon treated with ethinylestradiol *(54, 55)*, although the applicability of these studies to humans is not clear. Other contraceptive estrogens have not been studied.

More work has been done with diethylstilbestrol (DES), an orally active non-steroidal estrogen which

was administered to pregnant women in the first half of the 20th century to prevent miscarriage. The implication of DES in reproductive cancers in those women exposed *in utero* curtailed its use. Reports conflict as to whether this *in utero* exposure in humans also leads to altered patterns of sexual behaviour in adolescence and adulthood, or an increased risk of psychiatric disorders *(56–60)*. A recent nested case–control study comparing DES-exposed individuals and their unexposed siblings found no differences in psychiatric illness *(61)*. In rodent studies, female pine voles exposed to DES throughout gestation and lactation produced more aggressive female offsprings *(62)*. In another study, male rats exposed to DES neonatally showed decreased cell genesis in the hippocampus region of the brain *(63)*.

Bisphenol A (BPA), an organic compound found in polymers and plastics which can act as a weak estrogen mimetic, has also been studied. In studies exposing female rats to BPA during pregnancy, BPA abolished sexual differentiation normally observed in some exploratory behaviours *(64)*, and male offsprings exhibited increased aggression *(65)*. In rats exposed to BPA both *in utero* and through suckling, BPA abolished and inverted sex differences in learning and abolished normal sex differences in several brain regions *(66, 67)*. Finally, postnatal exposure to BPA led to disruption of the normal gender patterns of learning acquisition in male and female rats *(68)*. One study in non-human primates, in which BPA was administered to adult African green monkeys, demonstrated that estradiol-induced synaptogenesis was inhibited *(69)*.

The generalization of animal data to humans, and the application of evidence regarding DES and BPA to contraceptive estrogens present in human breast milk must be done with great caution. In particular, experimental doses of these compounds typically exceed doses found in breast milk by more than 1000-fold. Additionally, the biological activity of contraceptive estrogens in the brain has not been well described, and may vary among different compounds.

From these animal data, it can be concluded that the neonatal primate brain, including humans, has the capacity to be responsive to estradiol. Estradiol is capable of affecting all of the important processes of brain development, as is clearly delineated in the sexual differentiation of the male rodent brain, where estradiol is responsible for the key processes of both masculinization and defeminization. In all animal species examined to date, estradiol exerts these effects during a limited "critical period". If such a period exists in humans, its timing and duration is unknown. Little evidence exists delineating the effects of estrogen compounds found in contraceptives on brain development in humans or in animal models.

Effects of progesterone steroids on the developing brain

Dr Christine Wagner (University of Albany, USA) presented a review of evidence documenting the effects of progesterone on the developing brain. Interest in progesterone has lagged behind other steroid hormones, and thus, unlike estrogen, the body of evidence is severely limited in both humans and animal models.

Human studies are largely limited to the 1960s and 1970s, when women were administered synthetic progestogens for various indications during gestation. In some of the earliest of these studies, pre-adolescent and adolescent female offsprings exposed to progestogens *in utero* were noted to exhibit increased aggression *(70)*, personality features which, at the time, were described as male-typic ("tomboyism", preference for functional clothing, and prioritization of career over marriage) *(71)*, and ambiguous genitalia *(72)*. These outcomes were later attributed to the strong androgenic activity of these particular compounds. Later studies examining non-androgenic progestogen exposure *in utero,* particularly

medroxyprogesterone acetate, concluded that progestogens may have an anti-androgenic effect on the brain, given associations with preference for feminine clothing in exposed girls *(73)*, correlation with decreased physical activity in young boys, and decreased heterosexual activity in adolescence *(74)*. Studies from this same era also reported that girls exposed to progestogens prenatally had higher IQs *(73)*, were more likely to be standing and walking on their first birthday and exhibited greater academic achievement between nine and 20 years of age *(75)*. However, the failure of later studies to reproduce these findings has called the validity of these data into question. Most recently, in clinical trials performed in Germany, estradiol and progesterone have been administered in high doses to premature infants (infant plasma levels maintained at 200–600 µg/l of estradiol, and 300–600 µg/l of progesterone), to mimic *in utero* exposure at the end of pregnancy. Infants who received treatment were found to have improved bone development and lower rates of chronic lung disease when compared with controls *(76)*. In addition, at 15 months of corrected age, the psychomotor development index was normal in treated infants, but below average in untreated premature infants *(77)*.

Animal models may help elucidate the role of progesterone in the developing brain, but this body of research is in its infancy. As seen with testicular hormones (testosterone), the developing rodent brain is also likely exposed to progesterone. Prenatally, fetal rodent progesterone levels correlate to maternal levels. Postnatally, maternal progesterone levels are low after parturition, but quickly rise to a peak on postnatal day seven. This peak is negatively correlated with serum levels in the neonate, but the mediating factors of this relationship have not been described *(78)*. While it is possible that the developing neonate is exposed to progesterone ingested orally through nursing, the extent of metabolism, the nature of progesterone metabolites, and the amount of active substance presented to the brain are unknown.

Multiple regions of the rodent forebrain, midbrain, and hindbrain express progesterone receptors, suggesting that these regions would be sensitive to exposure to progesterone. *(79, 80)*. As was the case with estrogen receptors, progesterone receptor expression in several brain regions differs between males and females. The medial pre-optic nucleus, which mediates male reproductive behaviour in adulthood, is one such sexually dimorphic region of the rodent brain. Beginning a few days prior to parturition, and lasting until weaning, brains of male rats express significantly more progesterone receptors in this area than do female brains. This suggests not only that male brains are more sensitive to progesterone, but also that this sensitivity is limited to a critical period in sexual differentiation of the brain *(81)*. Blocking progesterone receptor activity during this period, accomplished in one study by administering progesterone receptor antagonist RU486 to rats during the first 10 days postpartum, significantly reduced the number of males showing sexual behaviour in adulthood *(82, 83)*. This is in contrast to studies conducted in the 1980s, in which progesterone administered to lactating female rats impaired sexual behaviour in their adult male offsprings *(84, 85)*. It is possible that not only must the brain be exposed to progesterone during a specific period of time postnatally, but that there is also an optimal level of progesterone receptor activity necessary for normal sexual differentiation, although this has not been proven. Brain regions that control gonadotropin secretion, specifically the anteroventral periventricular nucleus, also exhibit sex differences in progesterone receptor concentrations, although this effect is less well elucidated *(86)*.

In addition to sexually dimorphic regions of the brain, the developing cortex also transiently

expresses progesterone receptors during fetal and neonatal development *(87)*. The role of progesterone in cortical maturation is not defined, but it has been shown to be altered in progesterone receptor knock-out mice, which lack a functional gene for the progesterone receptor *(88)*. Progesterone receptors are also expressed in the dentate gyrus of the hippocampus perinatally *(80)*. This transient expression of progesterone receptors in the cortex and hippocampus suggests that progesterone may play a role in the development of these regions, and thereby influence later cognitive behaviours. Although less well studied, there is also evidence that perinatal exposure to progesterone alters learning in rats *(84, 89)*.

In conclusion, the neonatal rodent brain is sensitive to progesterone, and this sensitivity is anatomically and developmentally specific. Data suggest that exposure to exogenous progesterone during neural development, or alterations in timing, or level of progesterone exposure may alter development. Human data are limited, often of poor methodological quality or unable to be reproduced, and have produced conflicting results, rendering interpretation of the body of evidence difficult.

Conclusions

There is evidence that increasing birth intervals improves both the health of women and their children, making contraception after childbirth an important health issue. Among the contraceptive choices in the postpartum period are combined and progestogen-only hormonal methods. CHCs are linked to decreased milk production in women, and are currently not recommended for breastfeeding women for this reason. For most women, the health benefits of POCs clearly exceed the risks; however, the potential risks to newborns exposed to either of these hormonal contraceptives through breast milk have not been well described. The ideal hormonal contraceptive to use during lactation, and when it should be initiated, has been controversial, particularly in light of the contraceptive action provided by exclusive breastfeeding.

This consultation sought to address the unique challenge of considering the safety of contraceptive use in both the mother and her breastfed child. Discussions of safety focused on the importance of balancing the benefits of a mother's use of contraception with any associated risks to her infant. The consultation concentrated on the development of the brain, where the theoretical risks to the child are the greatest.

Available direct evidence for effects of maternal contraceptive hormone use on breastfed infants is limited. Studies indicate that exposure to contraceptive hormones through breast milk does not affect infant growth, weight, achievement of developmental milestones, or the incidence of episodes of illness. Although this body of evidence is reassuring, these data are severely limited by the short length of follow-up and small numbers of exposed infants studied, the use of varying, insensitive cognitive and development tests, the use of various contraceptive formulations, and the timing of contraceptive initiation. Exposure during the period of life when a child's metabolic capacity is at its nadir, and evaluation of subtle effects of contraceptive hormones on brain development, such as cognitive or behavioural changes, have not been evaluated.

Published data substantiate the presence of contraceptive hormones in breast milk, but the extent of absorption, metabolism and ultimate exposure to the brain in a breastfed infant is unclear. Neonatal metabolism is poorly described; however, the ability to metabolize drugs matures over time. Animal studies suggest that there is an effect of estrogen and progesterone on the developing brain. The exposure of the human

infant's brain to these hormones, and the effect of that exposure, if any, has not been quantified. Clinical studies to date have been inadequate to determine whether either serious or subtle long-term effects exist.

Recommendations

Current recommendations regarding use of CHCs in breast feeding women are largely based on the effect of these methods on maternal milk production. Adverse health outcomes or manifestations of exogenous estrogen in infants exposed to combined contraceptives through breast milk have not been demonstrated. However, studies have been inadequately designed to determine whether a risk of either serious or subtle long-term effects exists. The current WHO recommendation for CHC use remains unchanged:

- Use of CHCs by breastfeeding women during the first six weeks postpartum represents an unacceptable health risk, and the method should not be used.
- Between six weeks and six months postpartum, use of CHCs is usually not recommended for women who are breastfeeding. In many settings, pregnancy morbidity and mortality risks are high, and access to services is limited. In such settings, CHCs may be one of the few types of contraceptive methods widely available and accessible to breastfeeding women during this period.
- Beyond six months postpartum, advantages of using CHCs during breastfeeding generally outweigh theoretical or proven risks.

In view of the lack of data on the impact of progestogens on neonatal metabolism and the outstanding theoretical concerns of potential effects on brain development of the newborn, the current WHO recommendations for POC use remain unchanged. Although the currently available evidence does not demonstrate harm to exposed human infants, the expert consultation determined that unmeasured negative effects may well exist.

- Use of POCs, with the exception of the levonorgestrel-releasing IUD, is not usually recommended for women who are less than six weeks postpartum and breastfeeding, unless other more appropriate methods are unavailable or unacceptable.
- Beyond six weeks postpartum, there is no restriction for the use of POCs among breastfeeding women.
- The levonorgestrel-releasing IUD is not usually recommended for the first four postpartum weeks, unless other more appropriate methods are unavailable or unacceptable. Beyond four weeks postpartum, there is no restriction on its use.

In settings where pregnancy morbidity and mortality risks are high, and access to services is limited, POCs may be one of the few types of methods widely available and accessible to breastfeeding women immediately postpartum. Additionally, methods which require a skilled provider for initiation, such as the long-acting progestogen-only implants, may only be accessible at the time of delivery to some women.

POCs are highly effective and widely available methods of family planning, playing an important role in the contraceptive method mix. This is particularly so in regions with a high unmet need for contraception and where maternal morbidity and mortality are high. Any decisions regarding choice of a contraceptive method should also consider these facts.

Key evidence gaps

Given the importance of making POCs available to women who desire them, and given the outstanding theoretical concerns of potential effects on the newborn and the lack of data on this subject, WHO encourages further research in this area. Questions to be explored include:

1. What are the clinical outcomes, if any, in breastfed infants whose mothers used POCs in the neonatal period? Such studies should evaluate early exposure to progestogens through breast milk, utilize sensitive measures of cognitive and behavioural development, and follow participants throughout brain development, ideally through puberty.
2. What are the serum levels of POCs and their active metabolites in breastfed infants? In particular, research is needed to document these levels early in the neonatal period, when metabolic capabilities are developing.
3. How does the infant metabolize progestogens consumed through breast milk, and how efficient is that metabolism?
4. To what extent is the neonatal brain exposed to progestogens consumed through breast milk, or biologically active metabolites of progestogens consumed through breast milk?

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Summary report

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