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Is asthma an endocrine disease?

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The prevalence of pediatric asthma has increased in many parts of the world. This increase started more than 30 years ago and is particularly obvious in studies which document the onset of asthma in native populations when they change to a "Western" lifestyle. Besides a genetic influence, numerous environmental factors have been described for the development of asthma. Genetic factors are unlikely to explain the sharp increase within the short time period and also allergen and pollution exposure or any specific infection does not actually seem to be the main cause for this phenomenon. Another factor, however, that fits well into the geographical and temporal background of the asthma epidemic is the mother's oral contraceptive use. We therefore review the epidemiological association with later asthma in the children, give a summary of estrogen effects on immune function and develop a preliminary theory how oral contraception could influence later pregnancy.

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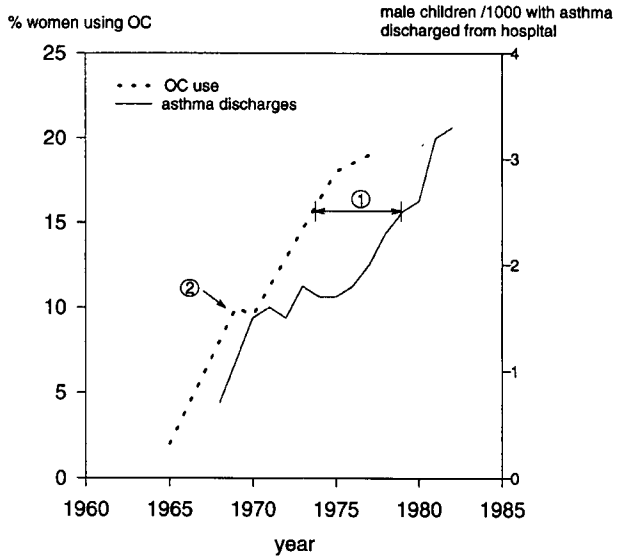
In many parts of the world, asthma has increased in prevalence and become the leading cause of chronic childhood disease (1). This increase, which was apparent already in 1970, has continued until now and is particularly obvious in studies which document the onset of asthma in native populations when they change to a "Western lifestyle" (2). Besides genetic influences (3) numerous environmental factors have been described for the development of asthma (4, 5). Population genetics, however, cannot explain the sharp increase in prevalence during the last three decades. So far neither allergen nor pollution exposure nor any specific infection appear to be the main causes for this phenomenon. Taking into account the heterogenous syndrome asthma and a more "fuzzy" interaction of minor risk factors, it is still likely that there are additional, hitherto unidentified risk factors (6).

Early onset allergic asthma, primarily in individuals born after 1960, makes up the largest proportion of the prevalence increase in Germany (7) but also in other countries (8). Therefore we were primarily interested in the prevalence increase in the youngest age group of children. Recent research indicates that children already at 22 weeks of gestation can mount immune responses to various environmental allergens such as egg or house dust mites (9, 10) which implies an antenatal exposure. There is some evidence that maternal exposure to house dust mite allergen during pregnancy could result in increased neonatal T cell proliferation to house dust mite allergen (11). Also sensitisation to seasonal allergens show a variation in children born over the course of a year (12). This view is further supported by the results of the first genome-wide scan for asthma and allergy genes where the strong maternal inheritance at several loci was interpreted as early immunological interaction of mother and child (13). In addition, a recent NHLBI workshop also confirmed the evidence that maternal asthma and maternal allergic rhinitis is more strongly associated with the risk of developing sensitisation in children and that this interaction occurs prenatally (14). It seems therefore reasonable to search for risk factors in early pregnancy in individuals born after 1960 that may be linked to a later manifestation of asthma. Moving the interest of early asthma induction to pregnancy, does not provide any obvious clues as there is no known risk factor in pregnancy that has been dramatically changed during the last three decades. Allergen exposure may have increased during this time period due to reduced ventilation in so called tight houses but there are no historical data for this theory. Is there any another factor?

Contraception methods, in particular hormonal methods of oral contraception (OC), have been dramatically changed during the last 30 years. OC containing a fixed dose of estrogen and progestogen in a 21-day regimen were introduced in the United States in 1960 and in Germany 1961, and were followed by a rapid dissemination in the early 1960s. In the evolution process, the monophasic combina-



① denotes the mean interval of 5 years that corresponds to the youngest age limit in this group of children.

② shows the adverse effect on OC use by a report by the "British Committee on the Safety of Medicine" concerning thromboembolism. The temporary decline seems to be also visible in the number of hospital discharges.

Fig. 1. Percent of women in Great Britain aged 15–44 years using OC (Population Report 1979) and rate of male children aged 5–14 years discharged from Welsh hospitals with diagnosis of asthma (Burr 1987).

tion gave way to the sequential pill and the "mini pill" of the 1970's with less than 50 μg oestrogen (15). The third generation uses different potent progestational agents: norgestrel, norethisterone and lynestrenol. Is there any epidemiological evidence that there is a link between OC intake and asthma in children?

The public data on world-wide OC use are too sparse for a formal meta-analysis. However, from an epidemiological view, it is remarkable that OCs were introduced around the same time as the prevalence of allergic diseases and asthma were rising (1). Fig. 1 shows the percentage of women taking OC on the left axis (taken from (17)) and – as annually repeated asthma surveys were not available for Great Britain – on the right axis the annual hospital discharge of children with asthma (16). There are a lot of fallacies of this kind of ecological observation, however, there are some more arguments supporting an association:

- The geographic trend with a higher prevalence of asthma in the Western societies compared to underdeveloped countries goes in parallel with OC use. This holds true for many countries in the world while the German East-West difference actually cannot be explained with the available data (18).
- There is an unexplained clustering of asthma in families by socioeconomic level (19) which could be related to OC use.
- In many cities asthma is more prevalent in cities (6) than the surrounding country where OC use is probably lower. (personal communication Britton, 1997).
- Children with three or more siblings are less frequently affected (20, 21). Together with the current infection theory, it is also likely that children in large families are less frequently exposed to any contraceptive method.
- The probandwise concordance rate even of dizygotic twins is considerably higher for asthma and allergic rhinitis (21, 22) than expected from sibling data (23). Sharing a common early environment could be a reason for this discrepancy.

The main question, however, is how can the lag effect between successful contraception and later gestation be explained? To develop any hypothesis we will first have to shed some light on the properties of estrogen and the early immunological development. Estrogen has by its ring structure several similarities to steroids and decreases ACTH. If estrogen hormone levels are disturbed a dramatic reduction in implantation rates occur (24). Following implantation the maternal decidua and the fetal extraembryonic tissues develop the feto-maternal interface (25). Interestingly, most of the cytokines associated with enhanced placental growth and fetal survival are members of the Th_2 family of cytokines (IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, GM-CSF and TNFβ) while those identified as deleterious (IL-2, IFNγ, TNFα) belong to the Th_1 family (26). Many of the cytokines, at least GM-CSF, IL1, IL6, TNFα are under control of the increasing amounts of estrogen (27). Even HLA-DR recognition by Fcε fragments is inhibited during pregnancy (28). PHA-induced lymphoblast transformation and *in vitro* cytotoxicity of NK cells seem to be decreased in women taking OCs (29, 30). Eosinophils are absent from the uterus of immature and ovariectomized rats but appear in large numbers in response to estrogen administration (31, 32). Although there is no clear shift towards any specific T cell development, multiple effects on maternal and fetal immune system by estrogens have been shown in the past.

How can any previous OC use on the actual pregnancy be explained? It is interesting to see that the first T cells appear in the thymus by 8 weeks and in the peripheral blood by 15–16 weeks of gestation (33). Therefore the minimum time interval to bridge is only 3 to 4 menstrual cycles (Fig. 2). Various mechanisms seem possible:

- *Semiacute effect:* The first possible mechanism is the selective implantation of embryos either by low estrogen levels immediately after OC

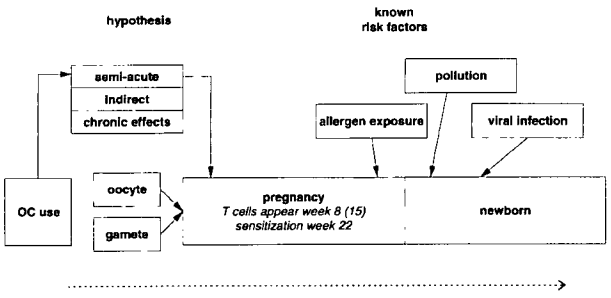


Fig. 2. Hypothesized timeline of factors influencing asthma and allergic diseases.

discontinuation or high levels by a rebound phenomenon. By escaping normal immunological rejection of the semi-allogenic embryo also "immuncompromised" embryos can survive. Another possibility to bridge a short time lag could be the influence on early cell division and differentiation of fetal immune cells by clonal selection or rearrangement of immune function genes.

- *Indirect effect:* There could be a longer lasting up-or-down regulation of receptors in the endometrial stroma cell. Estrogens could also induce an enzyme action in various organs that is still active even after OC discontinuation. A second indirect effect could be related to the fact that estrogens change the bacterial flora of the lower genital tract. Ascending infections affecting the placental parenchyma (villitis) or the chorionic membranes (local chorion amnitis) could influence the embryonic development by paracrine secretion of interleukins.
- *Chronic effect:* It could be hypothesised that ubiquitous environmental substances (DDE, PCB, flavonoids, dioxins) with estrogen like effects could also be involved (34, 35). However, the effective doses seem to be low (34). A similar problem arises also with current OC use where the pl· sma levels vary greatly due to large interind vidual clearance rates (36).

Which of these v 'hesised mechanisms is most convincing, is a m . r of opinion. It is concluded, however, that there is an effect of OC use on immune function (37, 38) and that a lag period of previous estrogen exposure until successful pregnancy could be overcome by at least three mechanisms.

Several additional questions arise. Are OCs really involved or is it any other type of contraception? Are there other concomitant factors of OC intake? Is it an effect of OC discontinuation? Which dose of estrogens or which combination of OC should be examined? Is the OC use at an early age of the mother more critical? Which time period could be relevant? Is there a particular withdrawal interval before the following pregnancy?

From a more clinical viewpoint there are also some arguments linking estrogen levels and asthma. During childhood more boys than girls are affected by asthma (39) while this ratio is reversed at puberty where estrogens play a more dominant role in girls. With the onset of puberty the frequency of hospital admission is higher among females (40). There is also a direct effect of estrogens on the airways. High levels of estrogen may modify relative levels of PGF_2 and PGE_2 (41). Estrogen and progesteron can influence free cortisol levels: Estrogen enhances the binding of corticosteroid binding globulin and progesteron by competition with cortisol for binding sites (42). Estrogen and progesteron also have been demonstrated to modify β-adrenergic receptor density in the rabbit lung (43). Women with asthma often experience subjective worsening of symptoms during normal menstrual cycling. About one third of asthmatic women reported more symptoms before or during menstruation (44–47) while not all studies have found such a relationship (48). Interestingly symptoms occur not on day 13 (highest estradiol concentrations) but on day 26 (lowest estradiol concentrations). During pregnancy asthma symptoms in some women improve, however, there is no consistent relationship (49, 50). A case history showed the development of asthma 4 years after taking OC which subsided after discontinuation (51) while a clinical study of seven asthmatic women did not find any difference of airway responsiveness during a 21 d course of OC (52). Finally, a prospective cohort study examining post-menopausal women showed a nearly threefold risk for adult onset asthma by current hormone replacement therapy (conjugated estrogens with or without progesterone) compared to premenopausal women (42). Among current users of conjugated estrogens, there was positive dose-response curve between daily dose and asthma risk. This is also a strong argument that OC or environmental estrogen like factors could relate to asthma induction. Is asthma an endocrine disease?

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