What we can learn from early blooming girls …

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The beginning of puberty and mammary gland development in girls is becoming increasingly common at an early or even very early stage (before the age of 8). But despite this precocious onset of puberty, the age at which menstruation occurs for the first time remains relatively unchanged or only moderately so. In boys, it has been observed that the final stages of puberty can occur later. These modifications show that, overall, the pubertal process is getting longer. Why take an interest in the age at which sexual maturity occurs and in variations in its duration? We should do so because, among other reasons, these events tell us a lot about the impact of the environment and certain pollutants on our organisms. Should we be worried?

Faced with some different ways in which puberty is developing and bearing in mind that it is such an essential process for human beings, researchers from Liège have reread and rectified some interpretations regarding this phenomenon that can now be classed as obsolete. They have also revealed exciting new avenues of investigation in two recently-published studies(1).

What were their objectives? They wanted to find an explanation for changes in the pubertal process and to decipher the underlying mechanisms involved in these changes. But among other things, they also wanted to interpret “the incredible and enormous individual variations in the times at which puberty occurs, with differences of up to five years between different individuals being observed”, explains Jean-Pierre Bourguignon, pediatric endocrinologist at the University of Liege and head of the associated unit at the Liege University Hospital Centre (CHU) and a member of Giga Neurosciences (University of Liege) and who participated in the two studies.
Sexuality is in the mind

The body of the child grows into that of an adult and this takes place over a (relatively long) period of his or her life. This is explained in the study that appeared in the journal *Frontiers in Neuroendocrinology*. Work carried out on rats made it possible to illustrate that the pubertal process in humans is "exceptional": in the context of a two-year life-span, the pubertal timing of rats varies from 4 to 5 days or 0.55% of its life. In practice, this period is eleven times shorter than in humans and primates... One of the possible implications of this observation is that the great variability in the age of onset of puberty and its long latent period between birth and this event are characteristic of the end of evolution of species. In practice, during this period the sexual organs and the other parts of the body also undergo changes including through a peak in growth because the growth hormone is produced in large quantities during this period. Fundamentally, this entire process is triggered by the brain, or more precisely, by the hypothalamus. Several factors determine the start of the pubertal process and also the great variability of the age of puberty and related phenomena in countries where life conditions are relatively equivalent. Among these factors genetics certainly play a role. But nutrition and environment, particularly in relation to the impact of pollutants and toxic substances as well as psychosocial stress, can influence or compete with this factor. For example, we now know that certain endocrine disruptors can directly stimulate the hypothalamic machinery earlier than the average anticipated age, independently of the genetic control and therefore trigger precocious puberty. The diversity of the causal factors, their development and their impact with regard to puberty, clearly increase the complexity of research into the phenomenon. But researchers must also take another element of vital importance into account: time. Certain periods of life are more receptive to the factors that lead to puberty.

Already in the fœtus...

In practice, the mechanism of pubertal development is triggered by hormonal changes in the brain. "We observe the redundancy of different systems that control the production of GnRH (gonadotropin-releasing hormone), a neuro-hormone that controls puberty and reproduction. A little like in a funnel, this small peptide which is produced in the hypothalamus by the neurones, is the ultimate activator of the pituitary, with a message produced at a certain frequency. This frequency makes it possible to determine the response by the pituitary. The pituitary releases the gonadotropins, which stimulate the development of the sexual glands. The activation of the pituitary gonadotropic cells occurs in three successive waves: once at the fetus stage, a second time shortly after birth (the "mini-puberty") and a third time at puberty."

At a certain age the endocrine glands (ovaries and testicles) become stimulated when they receive messages from the brain through the pituitary and they produce sex hormones which cause the body to undergo physical changes. The body changes, the bones get longer and muscles develop in the boys while adipose tissue develops in girls.

In girls, the ovaries begin to produce female hormones such as estrogen. The first sign of puberty can then appear in the obvious form of mammary gland growth. This usually happens between the ages of 8 and 13. The appearance of hair in the pubic area and under the arms as well as a peak in growth quickly follows this stage. Finally, the first menstrual period, called menarche, occurs. This usually occurs about two and a half years after the onset of puberty. Complete development of breasts marks the end of this process during which the young girl's pelvis becomes enlarged, her adipose tissue develops and is distributed differently in the body.
and her hips and buttocks become rounder. Regular ovulatory cycles however may not be seen before several years after menarche.

In boys, the first sign of puberty occurs with an increase in testicular volume, which is almost imperceptible to the individual and his family circle. This is in contrast to the development of breasts in girls. The testicles begin to produce testosterone and the appearance of pubic hair then follows, usually between the ages of 10 and 14. While the increase in testicular volume further progresses, the penis also becomes larger (between the ages of 11 to 12 years on average). As in the case of girls, the end of puberty, including the full development of pubic hair, only occurs several years after the first signs of puberty appear. Boys are different to girls in that the peak in growth is later during puberty (see the sixth-year primary-school class photo) accompanied by a change in the voice. They are now fertile, but certain changes in hairiness (face and/or chest) and muscle development can continue to increase thereafter. The last "detail" for both sexes: all these transformations can be accompanied by the development of acne, the appearance of body odor and mood changes.

Far from being a bed of roses

As we have seen, puberty follows a well-defined pattern of changes with these changes being correlated to different stages. We could therefore imagine that this process is a long one and though it is not necessarily a bed of roses, it is a relatively similar phenomenon in adolescents. Nothing could be further from the truth: large differences may occur, from the moment when this phenomenon appears, for the length of its duration to the time when it ends.

For a long time, the attention of researchers was focussed on girls and the increased age at which menarche occurs, the authors of "Changes in Pubertal Timing: Past Views, Recast Issues" remind us. In fact the scientific literature on the subject was largely preoccupied with an early onset of menarche. The phenomenon has been observed since the mid-19th century in many European and North-American countries, that is to say, in the so-called "developed" countries. According to observations, in one century, from 1850 to 1950, the first menstruations occurred four years earlier on average. "This represents a spectacular increase and has been interpreted as the consequence of an improvement in dietary hygiene", details Professor Bourguignon. However, following this line of logic, the first menstrual periods could have been expected to occur further earlier during the past fifty years among a majority of young girls. Moreover, projected figures predicted an average age of menarche of more or less 12 years of age at the end of the 20th century but this theory has not really been confirmed...

Slower than expected...

After the sixties, the advance of pubertal maturity slowed down and/or its decline stopped in a certain number of countries. During the last few years, the age of menarche has become relatively stable in countries such as Belgium. "For example", continues Professor Bourguignon, "A study conducted in Brussels in 1960 fixed the age of first menstruations at 13. Currently, we are still quite close to that age". Likewise, recent publications show that there is an increase in the average age of menarche - this is the case in Denmark or in Holland -, but it remains moderate.

So, has the time at which puberty arrives stopped changing? If the answer is yes, what is the reason? In fact, as Professor Bourguignon explains, "what we are noticing, is that the onset of puberty, with the development of mammary glands continues to concern more girls at an early age and even at a very early age (before 8
Yet despite this earlier onset of puberty, the age at which first menstruations are occurring remains relatively unchanged or only moderately so. The researchers point out that boys too are not unaffected by these changes. It has been observed that for them, the final stages of puberty can occur later. "These changes show that, overall, the pubertal process is getting longer", explains Professor Bourguignon.

This observation is certainly not insignificant: this lengthening of the pubertal process just like the heterogeneity of pubertal events, has led to revision of knowledge about the role and place of the different indicators and the mechanisms involved in pubertal onset. For example, the variations in the age of puberty can no longer be considered as the result of a complete separation of environmental and genetic determining factors: each of these plays a role, but associated factors also appear and these factors date from fetal life.

"We must be aware of the fact that it no longer suffices to say that puberty is occurring earlier and earlier. When we observe this trend, we back up our claims with clinical observations", says Professor Bourguignon. This point, which was also addressed in the article "Changes in Pubertal Timing: Past Views, Recast Issues", makes it possible to put into perspective the impact of studies based on self-evaluations by adolescents themselves who were asked to comment on their pubertal development.

Faced with young people who are often reluctant to allow themselves to undergo a physical examination - especially when this is not the reason they came to see the doctor in the first instance - many studies have been based on self-evaluation by adolescents. In order to gather information about young people, different methods have been developed. These are sometimes based on drawings, pictures or on different written propositions. In accordance with the validity of these methods which, it must be remembered, cannot entirely replace examinations by a qualified doctor, contradictory results have sometimes been obtained.
At the University of Liege, a retrospective self-evaluation study asked the respondents the following question: “Between the ages of 8 and 12, boys and girls change physically, but not at the same times. How would you compare your physical development with that of friends of the same age: very precocious, quite precocious, identical, a little later or much later”?

In the answers, many young people felt that they had experienced puberty earlier rather than later. Another study found the same results with 12 to 13% of adolescents admitting to experiencing puberty later than their peers and 28% felt that they had experienced puberty earlier than their friends of the same age. In reality, though two-thirds of the answers concurred with the medical diagnosis, for a large number of young people, things didn't add up.

This estimation can be explained quite "simply": describing themselves as "early" is more affirming for young people. And yet, detecting the proportion of young people confronted by precocious or later puberty remains an important fact for researchers. In fact, these adolescents are more likely to indulge in risky behaviour...

**The importance of nutrition**

Nutrition occupies an important place among the factors involved in the onset of puberty, particularly among girls. Logically, the link between nutrition and puberty has been the subject of many investigations. As the researchers point out, "the energy balance and pubertal timing share common regulatory factors with possible influences during fetal life".

From a theoretical point of view, we know that a sufficient level of adipose mass sends a signal to the neuroendocrine system to initiate puberty by means of leptin (in pubertal maturity, leptin plays a prerequisite role in neuroendocrine control). "Without leptin, puberty is not possible", explains Professor Bourguignon. "But having leptin does not necessarily trigger puberty". In any case, some authors have suggested obesity as a cause of precocious puberty.

In fact, the availability of energy and adiposity, in tandem with pubertal development, occupies an important role during several stages of life. Recent studies have shown that weight gain linked to variations in nutrition in the first months following birth can have an impact on both puberty and the risk of childhood obesity. Another study revealed that children who have a high body mass index (BMI) at 7 years of age reach puberty quicker. An opposite link was found between weight at birth and the advanced age at which menarche occurs: the lower the weight the earlier puberty arrives.

On this last point, research conducted on the impact of fetal and/or neonatal dietary restrictions show that the "organism will undergo changes during puberty in different ways according to the different conditions to which it is exposed", explains Professor Bourguignon. "A deficiency in nutrition that occurs in utero can be interpreted by the organism as a possible threat to the species. This can therefore be interpreted as a necessity to advance the age of pubertal maturity and the ability to reproduce". On the other hand, malnutrition around the time puberty is approaching can cause exactly the opposite effects. Under adverse conditions, the girl would get pregnant! To avoid such a situation the body thus would program a delay of puberty.

This extraordinary interpretation by the body of the conditions to which a fetus, newly-born or young child or girl is exposed, could also happen in the case of stressful psycho-social situations.

"The concept we are defending is the fact that a simple or simplistic relation cannot be made between nutrition and environment and pubertal timing", continues Professor Bourguignon. "In fact, everything depends on the moment when the different elements occur. It is precisely these different moments that can be a determining factor".

Moreover, the authors of the article that appeared in Frontiers of Neuroendocrinology state that the fact remains to be discovered, and this would appear to be the difficulty, whether there is a continuum between the three...
periods of sensitivity determined by the researchers - prenatal, postnatal and childhood, or whether each one acts "separately".

"What also needs to be borne in mind", continues Jean-Pierre Bourguignon, "is that during pregnancy, a nutritional imbalance because it is too rich or because it is insufficient can be stress factors, just as exposure to endocrine disrupters. We now know that the effects of these two factors are cumulative. During fetal life we programme the manner in which our energy balance will be regulated. The endocrine disrupters modify this basic system very convincingly: the run the risk, for example, of causing type 2 diabetes and obesity. But this can also influence puberty. One of our recent studies conducted on under-nourished rats during gestation showed that five days exposure to an endocrine disrupter (DES) changes the pubertal timing in tandem with a modification of the effects of leptin on the hypothalamus".

The adoption theory

The impact of nutrition and endocrine disrupter factors seems to be particularly crucial for some young girls: those who were adopted in distant countries (Read Precocious puberty and DDT). While examining the increased number of cases of precocious puberty in young girls, the researchers suggest that their earlier-onset puberty could be the result of a combination of adversity in early life followed by richness (nutritionally-speaking) at pre-puberty and in certain cases the impact (for them or their pregnant mothers)of exposure to chemical pollutants some of which are now banned in Europe... This is the case, for example, for children coming from countries with endemic malaria and where DDT is still used or has been widely used in the past. Boys and girls will be at a greater risk of precocious puberty in this case. In relation to Belgian children who are not exposed to these factors, the risk would be 80 times greater consider the pediatric endocrinologists.

"The moment is the poison"

Conclusions about the consequences of in-utero exposure to various pollutants and toxins have led researchers to other possible causes that are particularly important. "For a long time", explains Professor Bourguignon, "We have examined these environmental impacts from the angle of 'traditional' toxicology. We were adopting the principle of Paracelsus according to which 'the dose makes the poison'. Our research and others have shown that a change of paradigm is absolutely necessary: it is also true to say that the moment makes the poison. Thus, for example, the fetus will be sensitive to certain disrupters which, at other times of life would have no effect on the organism."

In an article soon to be published, the researchers from Liège also show that the same substance can have diametrically opposite effects, says Professor Bourguignon. In order to arrive at such a conclusion, they injected rats with different doses of bisphenol A, for a period of two weeks after the birth of these animals. In one case, it was the upper "limit"dose. This caused puberty to occur earlier. In the other case, a dose that was 200,000 times weaker, delayed puberty: the same substance given at the same time therefore had completely opposite effects according to the dose. By studying the frequency of neuropeptide secretion in the brain of the rats, it was possible to see that the brain of the animals exposed to high doses acted as though the animal was more mature, while conversely, a delay in maturation occurred with the weaker dose. If this study is important, it is so because it entirely calls into question the principle of "tolerable dose" for the organism.

"That principle, still defended by current toxicology, is not applicable to certain endocrine disrupters, Professor Bourguignon assures us. This assessment solidly shakes up of the system which we work with at the moment with regard to 'tolerance' of industrial products. Faced with the challenges, and in order to continue to
investigate this area that could potentially have serious consequences, the endocrinologist explains that the entire genome needs to be studied to see the expression of **genes** and their contradictory variations according to the doses of an injected substance. In fact, a reading of current works implies that there are possible links between the environment and genetic control, with different environmental effects influencing **epigenetic** mechanisms. "The possible modifications of the expression of genes during fetal life can extend to adult life and can then impact on later generations", warns the pediatric endocrinologist.

**Warn the citizens!**

Potentially, the work conducted on puberty can have extremely serious implications with regard to public health. "Currently, the fetus is exposed to more than a hundred toxic chemicals including endocrine disrupters", Professor Bourguignon reminds us. What attitude should the authorities have? Could they possibly resist the pressure from lobbies in the EU who fight for the right to be able to continue to use these substances? With regard to the states, we know that their opinions are sometimes divided with regard to the precautionary measures they decide to take. For example, in France, bisphenol A has been banned in all food. In Belgium, the authorities were content to ban baby foods. Another question remains to be answered in parallel with this: how to train doctors so that they can fully play a prevention role? "Currently, we can - we should - essentially say to women that pregnancy is a particularly delicate time during which the principle of precaution should be applied to the maximum", states Professor Bourguignon. "But this precaution does not only concern pregnant women: society as a whole should be aware that by dangerously exposing the fetus, we risk creating consequences whose effects will be felt in a few decades or more. As well as products, like for example phthalates, which can lead to genital malformations, a series of substances interfere with our hormonal system and are the precursors to a deferred problem. Studies show that this does not just affect puberty and reproduction: it can also lead to cerebral problems, obesity, diabetes, metabolic syndrome, cancer …"

The delay between our current reactions -or our insufficient reactions - and processes that are happening currently could have very serious consequences. From this viewpoint, the research conducted by the teams of researchers from Liège are a useful reminder that work on the modifications and stresses on puberty go over the heads of our boys with changing voices and our young girls blossoming into young women...

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Anne-Simone Parent, Delphine Franssen, Julie Fudvoye, Arlette Gérard, Jean-Pierre Bourguignon. "Developmental variations in environmental influences including endocrine disruptors on pubertal timing and neuroendocrine control : Revision of human observations and mechanistic insight from rodents" (Frontiers in Neuroendocrinology, 2015).