Biological clock and heredity in pubertal timing: what is new?

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Running title: Biological clock and pubertal timing

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We searched the PubMed database from the National Library of Medicine using the keywords "obesity," "nutritional status", "weight", "genetics", "hereditability", "epigenetics", "endocrine disruptors", "GnRH pulse generator", "kisspeptin", "MKRN3", "KDNy system," "prenatal exposure" associated with "puberty", "pubertal onset", "precocious puberty", "menarche", with limits set to only English-language articles. We included case-control studies, case series, reviews and meta-analysis published in English from 2006 to date.

Abstract

Puberty represents a milestone during a person's life and is characterized by several physical and psychological changes which end with the achievement of sexual maturation and of fertility.

Puberty onset depends on a series of sophisticated, not completely understood, mechanisms certainly involving Gonadotropin-Releasing Hormone (GnRH) and its effects on pituitary gonadotropins. As recent evidence has demonstrated that pubertal timing deeply affects future adult health life, much efforts have been performed in order to clarify the exact actors involved in the onset and progression of puberty. Genetic factors are undoubtedly essential players in the regulation of pubertal development, accounting for approximately 50-80% of its variability.

Mutations in genes such as KISS1, MKRN3 and DLK1 have been associated with central precocious puberty. Interestingly, a possible involvement of epigenetic mechanisms has been proposed as additional element able to affect pubertal phase. Environmental factors have recently attracted much attention. Indeed, an overall decrease in the age of puberty has been observed in the last decades. As genetic factors require long time to exert their effect, other players, such as environmental ones, may be involved. Special focus has been posed on nutritional status, endocrine-disrupting chemicals with non-conclusive results.

Pubertal timing deeply affects future life, suggesting the need to clarify mechanisms driving pubertal onset and progression, in order to identify tailored therapeutic strategies and targets.

Keywords: puberty, endocrine disruptors, genetics, epigenetics, environment

Introduction

Puberty is the period of transition from childhood to adulthood in which many physical and psychological changes sequentially take place until the achievement of sexual maturation and ability to procreate.

The Gonadotropin-Releasing Hormone (GnRH) represents the key hormone of reproductive function. Its pulsatile secretion controls the synthesis and release of pituitary gonadotropins LH and FSH, which in turn regulate gonadal function.

GnRH is produced by neurons distributed in a hypothalamic region including the septal area, the arcuate nucleus, and the preoptic area. These neurons derive from the embryonic olfactory epithelium and during fetal development show a peculiar migration along the olfactory nerves to reach their final hypothalamic location (1).

The hypothalamic-pituitary-gonadal axis is already active in the prenatal period, with a rise in gonadotropin secretion at mid-gestation.

Another increase in gonadotropin secretion called "minipuberty" is observed after birth and can persist for about 6 months in males and until 2 years in females. This increase has been related to the sudden drop in placental sex hormone levels and the subsequent loss of negative feedback on GnRH secretion.

Minipuberty provides a useful timeframe for investigating hypogonadism (1),(2),(3),(4).

After minipuberty there is a shutdown of the GnRH pulse generator until puberty. The mechanism that triggers the reactivation of the GnRH pulse generator and the subsequent onset of puberty is still unclear, but multiple factors are probably involved.

In males puberty normally begins between 9 and 14 years with the first sign represented by an increase in testicular volume that reaches 4 ml. In females, the onset of puberty ranges between 8 and 13 years of age and the first sign is the start of breast development (3).

In the last years an earlier onset of puberty seems to be observed, probably as a consequence of changes in nutritional status, increase in obesity rates and exposure to environmental factors such as endocrine disruptors (5), (6), (7).

The aim of this review is to summarize current available data on factors that may influence pubertal timing. Figure 1 summarizes factors that may potentially affect pubertal timing.

Neuroendocrine control of puberty

It is now known that the pulsatile secretion of GnRH is critical for gonadotropin secretion and the onset of puberty. Studies in various species have been conducted to characterize pulsatile LH secretion. In mammals, LH secretion seems to occur at a rate of 1 pulse/h during the follicular phase and 3-4 pulses/h during the luteal phase in females, while in males LH is released 2-3 times per hour (8). Pulsatile secretion is already active at mid-gestation in the sheep fetus and the LH pulse is also present in infancy in monkeys, sheep and humans (during minipuberty) (8). After this period there is a suppression of GnRH pulsatile secretion that lasts until the onset of puberty (8), (9).

This period of quiescence probably results from an interplay between the action of inhibitory signals and the switching off of excitatory signals (9), (10).

However, the precise mechanisms that regulate the disappearance of this inhibition, thus leading to the onset of puberty, are still unknown.

In the mature monkey, kisspeptin appears to stimulate LH secretion, because it is secreted episodically in the median eminence just before the GnRH peak (8).

Recent studies have shown that kisspeptinergic neurons constitute the key element of the pulse generator. Loss-of-function mutations of Kiss1 receptor are associated with pubertal delay and hypogonadism (11), (12), (3). On the contrary, mutations activating the receptor or mutations reducing the degradation of KISS1 have been described, albeit rarely, associated with cases of precocious puberty (13), (14).

There are two populations of kisspeptinergic neurons, the first is found in the arcuate nucleus in rodents and in the infundibular region in humans, the second in the anteroventral periventricular nucleus in rodents and in the preoptic area in non-rodents. Kisspeptinergic neurons in the arcuate nucleus also produce dynorphin and neurokinin. Recent studies have suggested a stimulatory role of neurokinin on kisspeptin, as inactivating mutations in the neurokinin gene or its receptor are associated with absence of puberty in men (15). Dynorphin appears to have an opposite role as the administration of a neurokinin receptor antagonist leads to puberty advancement in female rats (16). Furthermore, infusions of neurokinin and dynorphin receptor antagonists in sheep seem to suppress and stimulate LH secretion respectively (8).

It is therefore possible that kisspeptin, neurokinin and dynorphin are part of a single system (KNDy system) which, by integrating inhibitory and excitatory signals, sends signals to GnRH neurons. (8).

In mice it has been shown that Kisspeptinergic neurons have intracellular calcium oscillations every 8 minutes, while the GnRH/LH pulse occurs every 20 minutes. This means that these neurons are important but not the only modulators, and the presence of other neurons has been hypothesized as possible components of the GnRH pulse generator (9).

Herbison *et al.* (7) have also suggested the presence of other important elements in the generation of the LH pulse, defining the pulse generator as 'a group of intrinsically organized cells that generate intermittent periods of synchronous activity sufficient to generate a pulse of GnRH.

GABA, whose receptors are expressed on GnRH neurons, is a neurotransmitter that could provide an inhibitory signal for the brake occurring in the prepubertal period. In female monkeys, it has been shown that the increased GnRH release observed at puberty in the median eminence correlates with a reduction in GABA concentration in this region. Administration in the 3rd ventricle of a GABA receptor antagonist leads to early menarche and increased GnRH release (10).

Reduction of GABA at puberty is associated with increased expression of kisspeptin and glutamate. Glutamate-producing neurons would provide an excitatory signal; their expression and release of this neurotransmitter appear to increase during puberty. The administration of the glutamate agonist NMDA, causes early puberty in monkeys, suggesting that this neurotransmitter may be a component of the GnRH pulse generator (10), (9).

Novel insight into Genetic factors

Puberty is highly influenced by genetic factors. Perry and colleagues in 2014 identified, through GWAS studies, 100 loci on the human genome associated with age at menarche (17). In 2017 a major paper led to the knowledge of 389 independent signals conditioning age at menarche and explaining 7.4% variability (18).

A meta-analysis, collecting data on more than 200,000 men in the UK, identified 79 signals that affect the onset of puberty in men, defined by voice breaking or the appearance of facial hair (19).

It is known that around 50% of patients suffering from hypogonadotropic hypogonadism presents a genetic cause. Mutations of GNRH, ANOS1, DAX1, FGFR1, CHD7, FGF8, PROK2, PROKR2 genes have been associated with hypogonadotropic hypogonadism (20),(21). Mutation of different genes are responsible for combined pituitary hormone deficiency (LHX3, LHX4, HESX1, POUF1 and PROP1) (21). Cases of pubertal delay and hypogonadism were found in patients with loss of function mutations of Kiss1, Kiss1r, TAC3 and TAC3R (22), (12), (15), (11), (23). Recent evidence has shown the presence of mutations in interferon regulatory factor 2 binding protein (EAP1) in subjects with pubertal delay. EAP1 is normally produced in kisspeptinergic neurons and contributes to pulse generator activation through transactivation of the GnRH promoter. If silenced, it causes menstrual irregularities in female monkeys (9). EAP1 mutations (a deletion and a missense mutation) were described in two families of patients affected by pubertal delay (24).

The evidence of genetic mutations associated with precocious puberty has been growing recently, probably with the advent of new analytical methods,

To date, only one study has described a heterozygous gain-of-function mutation of the kisspeptin gene in a girl with precocious puberty. This mutation appears to cause a prolongation of intracellular Kiss1R signalling (25).

On the other hand, a missense mutation in the Kiss1 gene, which results in a kisspeptin form that is more resistant to degradation, was observed in 3 unrelated children with precocious puberty (1 boy aged 17 months, 2 girls aged 5.5 and 6 years). However, there are no other cases of precocious puberty associated with activating mutations of Kiss1 or Kiss1R, which therefore remain rare causes of central precocious puberty (26), (13), (14).

Other genes potentially involved in the etiopathogenesis of precocious puberty have been screened, but no causative mutations have been found (LEPTIN, LEPTINR, LIN28B, TTF1, EAP1, GABRA1, NPY1R, ERα) (27).

Through NGS studies, a heterozygous mutation of PROKR2 gene was found in a 3.5-year-old girl with precocious puberty. PROKR2 encodes for a G protein-coupled membrane receptor expressed on GnRH neurons, its activation promotes GnRH secretion. However, PROKR2 mutations seem to represent a rare cause of precocious puberty, as shown by a subsequent multicentre study that analysed 31 girls with idiopathic precocious puberty (aged less than 6 years) and did not find any PROKR2 variant (28).

Mutations in the genes encoding for makorin ring finger protein 3 (MKRN3) and delta like non-canonical notch ligand 1 (DLK1) have been identified as responsible for precocious puberty. These genes are maternally imprinted, meaning that the maternal allele is silenced and the paternal allele is expressed, so the causative mutations are inherited exclusively from the father. Single nucleotid polymorphisms (SNPs) of such genes are associated with early age at menarche (18).

MKRN3 gene is located in 15q11-q13, the critical region for Prader Willi syndrome (27).

MKRN3 gene expression appears to decrease abruptly before the onset of puberty, suggesting that makorin is a component of the inhibitory brake on GnRH secretion observed during childhood (9).

This role was confirmed in a recent study showing that makorin represses the activity of KISS1 and TAC3 (29).

Loss-of-function mutations of MKRN3 gene are associated with precocious puberty and appear to be the most common genetic cause of familial precocious puberty (33 to 46% of cases) (30).

To date, more than 40 frameshift, missense, nonsense mutations or mutations in the upstream promoter or regulatory regions have been described (31, 32). They are associated with a typical clinical presentation of central precocious puberty, with telarche and pubarche, early testis

enrlagement, accelerated statural growth, advancing bone age, high LH levels both basal and after GnRH stimulation. Females seem to be more severely affected than males, as the age of onset of puberty is much earlier in females (31), (25). A recent paper has evaluated clinical and hormonal features of a cohort including 45 girls and 26 boys with CPP due to MKRN3 mutations (33). Consistent with previous results, first pubertal signs occurred earlier in girls than boys. Additionally, in girls the presence of MKRN3 mutations was associated with a shorter delay between puberty onset and first evaluation and higher FSH levels than ICPP. Finally, the type of MKRN3 mutations was related to the extent of bone age advancement. The role of MKRN3 in nonsyndromic CPP has been further supported by a recent finding, showing the presence of whole gene deletions of MKRN3, paternally inherited, in two females referred for ICCP (34).

DLK1 is a paternally expressed imprinted gene located in 14q32.2 and encoding for a transmembrane protein; it is expressed in kisspeptinergic neurons and in various hypothalamic nuclei (26), (9).

DLK1 mutations (deletion or frameshift mutations), unlike MKRN3, were found in females mostly in association with a phenotype characterized by precocious puberty, obesity, insulin resistance, dyslipidaemia and type 2 diabetes mellitus.

Dauber in 2017 described a DLK1 gene defect (~14-kb deletion and 269-bp duplication) in 4 sisters with precocious puberty (age 4.6-5.9 years) (35). In the family history there was a grandmother with early menarche which, however, had not been investigated biochemically. More recently, DLK1 DNA sequencing performed in 60 women with precocious puberty led to the identification of 3 frameshift mutations in 5 women from 3 different families (36).

DLK1 seems to promote the differentiation of pancreatic ductal cells into β-cells and the synthesis and secretion of insulin. DLK1 may therefore represent a link between reproduction and metabolism (36). Figure 2 summarizes current knowledge on genes and factors involved in the modulation of puberty.

Novel insight into Epigenetic factors

Epigenetics refer to mechanisms which affect gene expression and cause hereditable changes without changing DNA sequencing. Differences in gene expression are heritable in the short term, though they do not involve mutations of the DNA itself, and seem to be fundamental for the development of health and diseases (37). The major epigenetic mechanisms include cytosine methylation, post-translational modification of histone proteins and remodeling of chromatin, and processes mediated by non-coding RNAs. Epigenetic regulation mainly consists of gene silencing, genomic imprinting and transcriptional regulation of tissue-specific genes during cellular differentiation (38).

Epigenetic mechanisms may be implicated in the regulation of GnRH secretion (39, 40), with most evidence derived from animal studies. By studying DNA methylation in monkeys, a decrease in methylation status of the GnRH gene's 5′ CpG island associated with an increase in GnRH mRNA levels across puberty has been observed (41). Data from experimental models have shown that manipulations of DNA methylation influence the onset of puberty (42).

The possible involvement of an epigenetic mechanism regulating Kiss1 gene expression during estrogen-positive feedback on gonadotropin-releasing hormone/gonadotropin surge was assessed in an experimental model (43); in particular an increased acetylation at the Kiss1 promoter in kisspeptin neurons due to the increased estradiol levels was found.
An epigenetic mechanism of transcriptional repression affecting the start of female puberty was found in animals (39) confirming that, though genetic factors are undoubtedly fundamental in influencing pubertal timing, additional players are involved.

The possible involvement of epigenetics in controlling puberty is supported by the observation that DNA methylation is fundamental for genomic imprinting which, in turn, is implicated in the regulation of puberty. Indeed, imprinted genes have been related with the age of menarche (17). More interestingly, loss-of function mutations of the imprinted MKRN3 gene are a recognized cause of familiar central precocious puberty (44). Genomic defects of DLK1 gene, another paternally expressed imprinted gene, have been associated with central precocious puberty in a Brazilian family (35). Additionally, an increased DNA methylation was reported in pubertal girls (45).

A recent paper has evaluated the relationship existing between DNA methylation profile and the timing of puberty by the analysis of methylome profile in girls with central precocious puberty and in a control group (46). Analyses were performed on 11 girls with CPP and 33 healthy controls (both prepubertal and pubertal) and demonstrated the existence of a broad pattern of DNA hypermethylation during normal and precocious puberty, consistent with the hypothesis that epigenetic changes occur during puberty, potentially accounting for the regulation of pubertal timing in humans.

A further epigenetic mechanism involves non-coding-RNAs including miRNAs. miRNAs are short noncoding RNAs that repress gene expression at the post- transcriptional level and are able to deeply affect many fundamental developmental processes. Though less investigated, recent findings suggest that microRNAs are involved in pubertal timing regulation, affecting for instance gonadotropin-releasing hormone (GnRH) neurons, which are crucial for puberty (47). Changes in the hypothalamic

expression of miRNAs of the let-7 family and the menarche-modulating gene, Lin28B, which suppresses the biogenesis of let-7 miRNAs, along the postnatal maturation preceding puberty have been reported (48). Interestingly, the increased expression of specific miRNAs in GnRH neurons during the infantile period is involved in the progression of puberty (47). A further evidence of the role of miRNAs in regulating puberty is due to the observation that miR-30 acts as a repressor of MKRN3, thus representing a novel hypothalamic pathway affecting pubertal onset (48).

Finally, metabolic and nutritional factors may influence pubertal timing by epigenetic mechanisms. Sirtuin 1 (SIRT1) has been described as a molecule able to restrain female puberty via epigenetic repression of the puberty-activating Kiss1 gene (49).

Overall, these findings suggest a role of epigenetics in controlling the complex mechanism regulating puberty onset and progression. Future studies are required to clarify whether and how, external factors such as nutritional status, endocrine disruptors or specific exposure during intrauterine life may affect puberty by epigenetic mechanisms.

Novel insight into Environmental factors

In recent years timing of puberty has been associated with long-term clinical outcomes and a broad range of diseases (50).

As previously discussed, genetic factors are fundamental players in determining the timing of puberty, accounting for about 50-80% of variances in pubertal timing. Recent evidence and the secular trend of an overall decreased age at puberty onset suggest a possible involvement of environmental factors (51), considering that the effects of genes require longer time to manifest.

Timing of puberty in girls has experienced some stabilization during the last decades of the 20th century, with a plateau reached by the age of menarche (51).
By contrast, an earlier onset of breast development has been recently reported (52). As it occurs without an apparent concomitant earlier age of menarche, a gonadotropin-independent estrogenic action at peripheral targets has been proposed as responsible for this discrepancy.
Puberty in males has been less investigated, partially due to the higher difficulties in assessing pubertal development in boys. Nevertheless, some data suggest that also boys experience an earlier onset of puberty (53).

Considering these trends, researchers started to investigate potential responsible factors. Unfortunately, as data are often not yet consistent and sometimes even conflicting, it is extremely difficult to establish a certain causal link.

Among the environmental factors able to affect puberty, nutritional status and a novel class of substances, named as endocrine-disrupting chemicals (EDCs), are likely the most investigated. Further factors include prenatal exposure to specific substances and physical activity.

A. Nutritional state and obesity

It is well known that obese girls have an increased risk of precocious puberty, while in males there are only few studies that provide conflicting data (54), (55), (56), (57), (58). Several years ago, Frisch and Revelle (59) suggested that a critical weight of 48 kg is necessary for the onset of menarche in women. Leptin, a hormone produced by adipocytes and necessary for regulating the sense of satiety and metabolism, appears to be the mediator that sends information on “critical” fat mass and energy status to the hypothalamus, thus stimulating activation of the GnRH pulse generator (60). Indeed, it has been shown that subjects with leptin receptor deficiency are affected by hypogonadotropic hypogonadism and that exogenous administration of leptin in these subjects induces puberty. This

may be due to a direct action of leptin on the hypothalamus, which may activate the GnRH pulse generator and stimulate gonadotropin production, thus suggesting a permissive role of leptin in the onset of puberty (9). However, there are also other factors linked to adipose tissue and involved in the regulation of pubertal timing. Indeed, weight gain also involves increased androgen production and aromatase activity resulting in greater conversion of androgens to oestrogens and increased exposure to oestrogens, which may promote earlier puberty in females and later puberty in males. Rapid catch-up growth in weight after birth, as seen in children born small for gestational age or undergoing dietary restriction in utero, may also result in an increased risk of obesity, impaired body composition and insulin resistance (61). Insulin resistance seems to reduce SHBG levels, thus increasing sex hormone bioavailability and sending positive feedback to the hypothalamic-pituitary-gonadal axis to produce gonadotropins. Rapid weight gain during childhood is also responsible for higher androgen levels, which may accelerate the onset of puberty as seen in children with congenital adrenal hyperplasia (CAH). It is well known that conditions of nutritional stress are responsible for delayed onset and progression of puberty. The link between nutritional status and kiss1 expression could be represented by several energy sensors including the mammalian target of rapamycin (mTOR), the AMP-activated protein kinase (AMPK), and sirtuin. mTOR is usually active under conditions of energy excess and stimulates anabolic processes, whereas AMPK and sirtuin are active under conditions of caloric restriction and activate catabolic pathways, while they inhibit anabolic pathways. Indeed, studies conducted in mice have shown that during undernutrition, associated with low leptin levels, the activation of the AMPK pathway and the inhibition of mTOR signalling lead to reduced Kiss1 expression and delayed puberty (9), (62). Additionally, sirtuin potentiates the repressive action on kisspeptin, interacting with Polycomb silencing complex (49). Conversely, early exposure to high caloric intake, associated with high levels of leptin, leads to reduced sirtuin levels in arcuate nucleus neurons, kiss1 activation and advancement of puberty. The role of the mTOR/AMPK system in accelerating puberty during excessive energy intake remains to be elucidated (62).

B. <u>Endocrine disruptors</u>

Among the environmental factors, which potentially perturb hormonal systems and affect puberty, Endocrine disruptors have attracted attention in the last years and have been proposed as at least partially responsible for the observed secular trend. According to the current available definition, an endocrine disrupting chemical (ECD) is “an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action” (63). Therefore, ECDs are a class of heterogeneous exogenous compounds which act as hormonally active products and, by binding to hormone

receptors, may exert multiple actions affecting the function of peripheral target tissues or directly influencing central axis (64). Typically, ECDs act by interfering with hormonal binding to specific receptor, such as androgen or estrogen receptor and play as agonists or antagonists; their biological half-lives vary greatly, with some being detectable for a long time whereas others measurable just for a short time, but with effects which can persist for a long time. The consequences of ECDs actions seem to be extremely wide and difficult to be precisely defined, especially in terms of causal links. Most difficulties rely on the wide range of substances spread in environment, the different concentrations, the possibility of a direct contact with human beings, or of a persistent exposure with the environment containing them, and the potential different effect depending on the window of exposure. In this regard, the exposure during a particular susceptible time, such as intrauterine or early post-natal life, may be critical (65). Overall, the actions of these compounds seem to be sexually dimorphic, compound specific and influenced by the window of exposure (53). Most available data about ECDs and puberty derive from animal models, though effects of EDCs have been investigated also in humans, with the majority of data obtained in females but also investigated in relation with fetal testis development, male puberty and parameters such as penile length and testicular volume. Results differ depending on the class of ECDs.

Polybrominated diphenyl ethers (PBDEs) are a class of compounds present in a wide range of products. PBDEs have been found as contaminants in environmental and human tissue samples and different experimental models have shown that PBDEs have endocrine disruption properties. Data obtained in humans are not univocal. A recent study has demonstrated a relationship between increased levels of BPDEs and premature telarche in Italian girls (66), confirming estrogenic action of this class of substances, in agreement with previous findings (67), without effect on the hypothalamic-pituitary-gonadal axis, as suggested by the lack of association with central precocious puberty. Different PBDEs were measured in maternal serum during pregnancy or at delivery as expression of prenatal exposures. Additionally, childhood exposures were evaluated by dosing PBDE at 9 years of age in a cohort of 309 boys and 314 girls. The results showed that prenatal PBDE exposure was associated with later menarche in girls and earlier pubarche in boys (68).

Polychlorinated biphenyls (PCBs) are a class of industrial chemicals previously widely used, stored in fat tissue and abundantly present in the environment. Data regarding their relation with pubertal development are conflicting as PCB exposure doesn't seem to be related with the timing of puberty in girls, whereas in males PCB exposure has been associated with delayed puberty (69). In particular, by studying 80 boys who were exposed during pubertal time to PCBs and dioxin, a negative relation between higher PCBs exposure and genital maturation and pubic hair presentation was found while

no link was found with dioxin. By contrast, PCB exposure studies proved conflicting relationships with male hormones (70).

Phthalates include a large group of compounds present in products ranging from plastics, to coatings, cosmetics, medical tubing, personal care products, vinyl flooring materials, and toys. As a consequence, they are ubiquitous. In animals, consistent data support their endocrine disrupting properties; less evidence is present in humans. Pre-pubertal exposures to phthalates and BPA were associated with pubertal timing in children, particularly in girls whereas inconsistent associations were reported in boys (71). A recent paper conducted on a cohort of 87 girls with precocious puberty and 63 controls showed a positive association between phthalate exposure and incidence of precocious puberty in girls, so that authors suggest that a reduced exposure to phthalate esters could represent a health strategy (72). Another report found that an oxidative metabolite of several parent phthalate diesters was associated with delay of both breast development and menarche (73). Different molecular-weight may be responsible for different clinical outcomes and the effects of phthalates.

Bisphenol A (BPA) is extremely widespread worldwide as a precursor of some plastics and chemical additives, and present in products ranging from plastic bottles, food storage, containers, baby bottles, and CDs. Urinary concentrations of BPA were higher in girls with premature telarche compared to controls (74) as well as with increased odds of having central precocious puberty in girls (75). Another cross-sectional study performed on patients with advanced puberty and controls suggest that BPA exposure appears to be related to an earlier age at onset of puberty especially in obese girls (76). A possible mechanism by which BPA may influence puberty may depend on its capability to affect metabolism. As Chinese girls with detected BPA were more likely to have delayed menarche compared with girls with undetectable BPA (77), BPA effects on female pubertal development is still unclear. In males, data on the relation between BPA and puberty are inconsistent (78).
An additional factor which has to be taken into account derives from the importance of early life phases in influencing later development of puberty. Therefore, the exposure to environmental pollutants during particularly vulnerable moments, such as fetal life, may influence the following onset and progression of puberty and eventually the reproductive system, with higher risk for later negative outcomes. First evidence of a possible role of early life exposure to EDCs on pubertal timing derived from the observation of a higher risk of sexual precocity in children early exposed to DDT and then migrated to Belgium for adoption compared to Belgian native children (79, 80). Consistently, a link between early exposure to a metabolite of DDT and early menarche has been reported (81). Data on males are few and less consistent (79).

Overall, these data show the difficulty in studying ECDs and in assessing their causal link with pubertal onset and progression. The few available findings in humans provide not conclusive results, in disagreement with more consistent results obtained in animals. Future studies are undoubtedly required to clarify the link between specific compounds and pubertal clinical outcomes. Additionally, as ECDs may act by influencing epigenetic regulation which, in turn, may account for negative effects showed by exposed individuals and following generations, longitudinal studies with long-term follow-up are required to verify this hypothesis.

C. Prenatal exposure and other factors

A possible role of intrauterine life events on pubertal clock has been proposed. The mechanisms by which intrauterine life may influence pubertal development are not fully understood and may involve different actors, including epigenetic mechanisms. An earlier menarche age was reported in case of low birth weight or IUGR but data are not conclusive and the relationship between anthropometric variables at birth and the age of pubertal development remains unclear as conflicting results have been reported (82). ~~Prenatal exposure to specific factors may influence puberty, as~~ early menarche has been associated with mother's smoking, diethylstilbestrol exposure during pregnancy, pre-pregnancy diabetes, and pregnancy-related hypertensive disorder (83). Nevertheless, data aren't yet conclusive. For instance, the association between pubertal timing and the presence of maternal diabetes is uncertain (84), as well as the exposure to drugs such as glucocorticoids in utero was not associated with earlier puberty for either boys or girls (85).

First life phases deeply affect later health. Events occurring in this period may be, at least partially, involved in the regulation of puberty. Early life factors reported to be associated with earlier menarche include higher growth rate during childhood, higher childhood socioeconomic position, family conflict and parental divorce and presence of a stepfather (86). Notably, a recent study performed on animals has shown that lactation represents a critical window for the development of normal metabolic and reproductive function in offspring and that maternal high fat diet during lactation caused early puberty associated with altered gut microbiota of the offspring. Interestingly, microbial reconstitution was able to stop pubertal changes, suggesting that it may represent a therapeutic option to manage early puberty associated with insulin resistance (87).

As association does not imply a causal link, further studies are required to clarify this relationship.

Pubertal timing and COVID-19

Finally, pubertal timing seems to be influenced by additional factors such as childhood physical activity, though the true relationship is difficult to be defined as likely confounded by concomitant changes in diet and lifestyle (88).

These factors may be responsible for the association emerged between puberty and Coronavirus infection. Last year a novel coronavirus infection spread all around the world deeply influencing global population's lifestyle (89). Notably, an effect on puberty has been reported by two different groups. Stagi et al firstly reported an increased incidence of central precocious puberty and a faster rate of progression in girls with a previous diagnosis during and after lockdown, compared to the rates of previous years (90). Especially at the onset of COVID-19 pandemic when a strict lockdown was used to limit the widespread of Sars-Cov2, life habits were deeply affected and these changes may be implicated in influencing pubertal onset and progression. In particular, an increased use of electronic devices as well as reduced physical activity with consequent increased BMI may be involved. Additionally, authors speculated that psychological factors may be involved.

Unfortunately, authors do no report data on males, thus preventing from assessing whether these environmental factors may influence puberty in boys as well.

An increased rate of precocious development has been confirmed by another Italian group (91), which reported a significant increase of precocious puberty cases in girls during the first period of COVID-19 pandemic, likely related to the above mentioned factors.

Conclusions

Puberty is one of the most critical phases of life, which appears to influence later trajectory of individual life. Timing of puberty seems to rely on many factors, among which genetic factors undoubtedly play a major role. In females, the secular trend has led to a progressive reduction of age at menarche from the mid of 19th century to the mid of the 20th century. After that, a sort of stabilization has been observed for age at menarche, but an earlier onset of breast development and an overall decreased age at puberty onset has been reported. In males, though with less consistent results, an anticipated onset of puberty has also been observed. As genetic changes require centuries to occur, other factors able to exert their effects in a shorter period should be considered. Several actors have been hypothesized, though conclusive findings are far to be reached. Endocrine disruptors, nutritional status and lifestyle habits have been involved. Compelling evidence suggests that factors acting during intrauterine life as well as in early post-natal life are also important.

Considering the relevance of the pubertal window for the psychological and physical health of a human being, additional efforts are needed to define the exact mechanisms underlying the onset and the development of puberty.

Authors' Contributions

FB and EI collected published data and drafted the manuscript; MCN, AC and AG contributed to the design of the study and critically revised the manuscript, LDS and CB conceived the study, participated in its design and coordination and critically revised the manuscript. All authors read and approved the final version of the manuscript.

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Captions to figures

Figure 1: Factors potentially affecting pubertal timing

Figure 2: Modulation of pubertal timing