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Is polycystic ovary syndrome a 20th Century phenomenon?

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Abstract

Polycystic ovary syndrome (PCOS) affects around 10% of women of reproductive age and is most common in developed countries. The aetiology of PCOS is not completely understood. Current evidence suggests that the syndrome results from a genetic predisposition interacting with developmental events during fetal or perinatal life that together increase susceptibility in some individuals. This implies that environmental factors influence the initiation of PCOS in the fetus or infant, either directly or via the mother. PCOS is often considered to be an ancient disorder but there is no direct proof of this in the medical or historic record. One of the cardinal features, polycystic ovaries, was first described only in the early 1900s, despite reports of many thousands of autopsies recorded earlier. This conundrum could be explained by postulating that polycystic ovaries were rare before the 1900s and have become more common over the last 100 years. The hypothesis that PCOS is a syndrome of the 20th Century would eliminate the need to explain the paradox of why there exists a genetic predisposition to subfertility syndrome.

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Introduction

Despite its common occurrence and substantial co-morbidities, including type 2 diabetes and obesity, polycystic ovary syndrome (PCOS) is very poorly understood. Research effort to define the pathophysiological origins of PCOS is urgently needed. There are a number of scientific conundrums surrounding PCOS including its developmental origins and aetiology that have hampered progress and provoked debate in recent years. Here, we discuss these and present a counter concept suggesting that PCOS is a syndrome that has emerged to become a more frequent event in the 20th Century. If this postulate is true, there are major implications for how we investigate the pathophysiological mechanisms and aetiology of PCOS and its co-morbidities. A better understanding of how environmental factors and genetics interact, and the nature of the critical environmental exposures, is required to develop effective syndrome-specific interventions and treatments.

What is polycystic ovary syndrome?

The name 'PCOS' focuses on just one diagnostic feature – polycystic ovarian morphology – which is a misleading description of the ovarian features [1]. Women with PCOS often believe they have multiple ovarian cysts based on the name of the condition. However, the 'cysts' are actually egg-containing follicles that arrest during follicular growth [3]. While polycystic ovaries have an elevated number of follicles and more stromal tissue containing more collagen [2], this is only one diagnostic feature of the syndrome of PCOS. Note that in this article we critically distinguish the discussion between the syndrome of PCOS, and the clinical feature of polycystic ovaries.

The majority of women with PCOS have elevated androgen levels due in large part to the increased number of antral follicles containing thecal cells that hypersecrete androgens [3]. They therefore exhibit symptoms of excess androgen (hirsutism, acne, central adiposity) and not only experience infertility (menstrual irregularity, anovulatory infertility, miscarriage) but also have substantially increased risk of becoming obese, insulin resistant and of developing type 2 diabetes, non-alcoholic fatty liver disease, dyslipidaemia and depression [4]. Women with PCOS have at least a four-fold increased risk of type 2 diabetes, even without taking into account their additional predisposition to becoming overweight [5], [6]. Thus PCOS can be considered a syndrome where hormonal underpinnings cause both reproductive and metabolic features.

Diagnostic criteria for PCOS have evolved following meetings of experts in 1990 hosted by the NIH [1], in 2003 in Rotterdam [7] and subsequently by the Androgen Excess Polycystic Ovary Syndrome Society [8]. Evidence-based guidelines for diagnosis and treatment have been developed [9], [10] and focus on the combination of key features including oligo or amenorrhea, evidence of androgen excess and polycystic ovarian morphology.

What are polycystic ovaries?

Polycystic ovaries exhibit several features that include multiple growth-arrested follicles, an extremely thickened ovarian capsule or tunica albuginea, and an increased amount of ovarian

cortex with elevated collagen content [2], suggesting a more fibrous composition. Surprisingly polycystic ovaries were only first described in 1928 by Lesnoy [11] and by Stein and Leventhal in 1935 [12]. The original publication by Lesnoy [11] was published in Russian. An English translation and a copy of the original article are provided in the Supplementary Information. Both studies describe the hallmark features of polycystic ovaries. Interestingly both studies describe utilising wedge resection as a treatment. Remarkably, variations on this treatment are still sometimes used for treatment of infertility of women with PCOS [13].

A recent community-based PCOS-prevalence study was conducted on 728 women born in Adelaide, Australia with an average age of 30 years [14]. Of these women, 277 were selected for further examination of PCOS symptoms. Amongst these, 108 had transvaginal ultrasound and the presence of polycystic ovarian morphology was identified in 41 of these women $[(41 \div 108) \times 277] \div 728 = 0.144]$. Thus it was found that 14.4% had polycystic ovaries. A prevalence estimate of polycystic ovaries was 17.6% in another study in Turkey [15]. An earlier study in women randomly selected from the electoral roll in New Zealand with an average age of 33 years found the prevalence of polycystic ovaries to be 21% (39 out of 183 women diagnosed by ultrasound) [16]. Consistent with this, a UK study identified polycystic ovaries in 23% of women [17]. It should be noted that the prevalence is age dependent, with a lower incidence of polycystic ovaries in older women [18].

Are polycystic ovaries a recent clinical entity?

The high current prevalence of polycystic ovaries in Western populations raises the question of why polycystic ovaries were only first recognised in the early 1900s [11], [12]. Quotes from a number of earlier publications allude to symptoms in women that could be due to the syndrome of PCOS [19], [20], but these symptoms could also be due to other causes. We contend that the prevalence of polycystic ovaries is particularly relevant to estimating the historic incidence of PCOS, since, although this feature alone does not satisfy current clinical definitions of PCOS, it is a feature most commonly associated with PCOS and less likely with other conditions.

If PCOS existed in the early 1900s at the same prevalence it does today, it is difficult to explain why polycystic ovaries were not described much earlier. A few possibilities could explain this. First and most obviously, polycystic ovaries are now readily diagnosed by ultrasonography, and this technology was not commonly available until the 1960's. However, polycystic ovaries are easy to identify on laparotomy or autopsy by mere visual observations as they are larger, full of follicles and fibrous [2]. Another possibility is that autopsies were uncommon prior to the early 1900s. On the contrary, human autopsies have been conducted at least since the time of Galen (130–216). One famous Bohemian pathologist Rojitansky (1804–1878) was reported to have conducted 30,000 autopsies [21] and he described his opportunities to examine ovaries as 'very extensive' [22]. King and Meeham [21] writing on the history of autopsies state that '*In the sixteenth and seventeenth centuries very many autopsies were performed and recorded. One of the great medical compilations of all*

time is the Sepulchretum of Theophilus Bonetus (1620–1689), first published in 1679. The second edition, cited herein, appeared in 1700, in three folio volumes. These volumes collect over 3000 autopsies, reported in varying length from a few lines to half a folio page or sometimes more. Some 450 authors are represented, ranging from Galen to the physicians of the late seventeenth century. All the outstanding physicians of historic note are included – Bartholin, Fallopius, Fernel, Harvey, van Helmont, Malpighi, Paracelsus, Pare, the Riolans, Sennert, Vesalius, Wepfer and Willis, to name but a few.' Later with the development of modern hospitals and the increasing use of histology, autopsies became common-place. Bichat (1771–1802), who is regarded as the 'Father of Histology', was reported to have conducted 600 autopsies in one year alone [21]. So why is it that polycystic ovaries were not described prior to the early 1900s?

Some explanations could invoke a predominance of male over female autopsies, or failure to examine female reproductive tissues, but these are not tenable. There are regular reports of female autopsy on the historic record, and these often report irregularities of female reproductive tissues and organs [23]. Also historically, autopsy patients were more likely to be of people of reproductive age because lifespans were shorter than today. Moreover, given that polycystic ovaries are clearly evident and visible to the naked eye [2], it seems unlikely that experienced physicians would overlook this irregularity.

With so many opportunities to record the presence of polycystic ovaries at autopsy over centuries before their first description in the 1900s, it is reasonable to conclude that polycystic ovaries were previously so rare as to not have been documented. Certainly, the sentinel publications by Lesnoy and Stein and Leventhal give no indication that this ovarian morphology was previously known to the medical literature. Stein and Leventhal clearly believed they were describing a new entity when they said 'According to the same authoritative works, little or no mention is made of bilateral polycystic ovaries accompanied by amenorrhea….' [12]. We suggest the possibility that polycystic ovaries were so rare before the 1900s as to be only first described adequately in the early 1900s, in which case PCOS is a syndrome that arose largely in the 20th Century.

Current issues on the genetic origins of PCOS

Currently the cause(s) and aetiology of PCOS are not known. Early studies of PCOS found familial linkage and subsequent twin studies identified a sizable genetic component to the heritability of PCOS [24]. GWAS and microsatellite linkage studies have identified a number of loci associated with PCOS [25]. The genes closest to loci identified as predisposing to PCOS include *FBN3*, *DENND1A*, *LHCGR*, *THADA*, *C9orf3*, *FSHR*, *HMGA2*, *INSR*, *RAB5B*, *SUMO1P1*, *TOX3*, *YAP1*, *ERBB4*, *FSHB*, *GATA4*, *KRR1* and *RAD50* [see review [26]]. The prospect of genetic causes of PCOS has triggered much discussion about how genes leading to reduced fertility could be maintained within a population [27], [28], [29], [30], [31]. Rationally they would normally be eliminated by natural selection unless they confer other advantages to survival of the offspring. However, none of the genetic loci identified confer an obvious survival advantage.

As noted earlier, PCOS has been suggested to be an ancient syndrome [19], [20], [27], [31]. If this were the case, an alternative explanation for PCOS susceptibility genes surviving at low frequency in a population might be that they confer an attribute to provide a survival advantage under specific environmental conditions, and that these conditions have since changed to cause the emergence of PCOS as a common phenotype. In this view, the long term evolution of phenotypic stability under constant environmental conditions, referred to as canalisation, could have been disrupted, permitting the expression of underlying cryptic genetic variation from natural selection or mutation [32]. As a consequence, PCOS may be viewed as a conditional phenotype whereby a specific set of environmental conditions has unmasked a normally unexpressed genetic pathway, which may provide a survival advantage under certain conditions, but which offers no advantage and possibly a serious disadvantage in prevailing conditions.

We have considered an alternative explanation for how genes associated with a subfertility syndrome such as PCOS persist in a population, namely that if the current high prevalence of polycystic ovaries and PCOS has only just emerged just over 4 generations ago in the 1900s, then there has been very little time for negative selection to occur.

Environmental and fetal origins of PCOS

There is also evidence of a fetal epigenetic origin [33], [34], [35] of developing a predisposition to PCOS, and the challenge is to define a pathophysiological mechanism that accommodates a contribution of both genetic and environmental determinants. A fetal or perinatal origin implies the action of environmental influences [36], [37], but the nature of these factors and their target genes and tissues are unknown. Many new industrial processes, dietary constituents, food preservation and cooking methods, and new environmental chemicals, toxins and drugs have emerged and permeated human culture since then. Any one of these, alone or in combination, might be a candidate causal agent – and several have features, biological actions and exposure patterns that warrant investigation.

It is interesting to note that many other non-communicable metabolic diseases with epigenetic origins are known to be increasing in prevalence as a result of modern lifestyle factors and environmental insults affecting fetal and infant development [38], [39], [40]. Many of these agents impact susceptibility to disease later in life through common pathways, notably as endocrine disrupting chemicals [41], or as pro-inflammatory insults that alter the microbiome and immune function [42]. It is possible that environmental factors contributing to PCOS susceptibility overlap with those contributing to obesity and metabolic disorder, but complete congruency seems unlikely, as PCOS often precedes and can occur independently of overweight and obesity [43].

Implications of PCOS as a 20th Century phenomenon

One might assume that epidemiological research methodology will allow systematic identification of candidate causal agents, but the complexity of establishing cause-and-effect relationships is challenging. For example, many decades of work were required to identify tobacco smoking as responsible for the epidemic of lung cancer arising in the 1920s, amongst the list of other possible candidates including 'asphalt dust from newly tarred roads, industrial air pollution and latent effects from exposure to poison gas in the First World War or the global influenza pandemic' [44]. Identifying an environmental cause of PCOS would be particularly difficult if the effector(s) is operating at a specific stage of fetal or infant development.

In conclusion, we urge researchers investigating the origins and aetiology of PCOS and its co-morbidities to consider at least the prospect of a relatively recent, environmental cause(s) of PCOS. To investigate this hypothesis we suggest a multi-disciplinary strategy to identify links between candidate environmental agents and PCOS incidence, to develop useful experimental models that allow evaluation of causal triggers and mechanisms, and a focus on research that investigates biologically plausible pathways linking the known fetal and neonatal developmental changes with the adult manifestation of the syndrome. Only when these pieces of the puzzle are in place will we be in a position to devise public health approaches and associated interventions to protect future generations from PCOS.

Disclosure summary

We certify that none of us have a conflict of interest that is relevant to the subject matter or materials included in this work.

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Conflict of interest

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Author contributions

L.S., D.L. and K.H. translated the original article by Lesnoy and they and R.J.R., M.D., H.F.I-R. and S.A.R. contributed to the discussion of the content, wrote the article and reviewed and/or edited the article before submission.

Competing interest statement

The authors declare no competing interests.

Appendix A. Supplementary data

The following are the Supplementary data to this article:

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Supplementary data 1.

Recommended articles Citing articles (0)

Research data for this article

Data not available / No data was used for the research described in the article

About research data

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