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Invited review

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Polycystic ovary syndrome and hyperglycaemia in pregnancy.
A narrative review and results from a prospective Danish cohort study.

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Abstract

Background: Insulin resistance is common in polycystic ovary syndrome (PCOS). PCOS may be associated with increased risk of gestational diabetes mellitus (GDM).

Objectives: To 1) review literature regarding PCOS and hyperglycaemia in pregnancy and 2) present original data from Odense Child Cohort (OCC) regarding GDM in PCOS.

Methods: Literature search including original studies from 2000-18. OCC included 2,548 pregnant women, 9.5 % (n=241) had PCOS. Fasting plasma glucose was measured in 1,519 and 659 oral glucose tolerance tests were performed (with risk factor for GDM, n= 384, without risk factors, n=275), applying two different GDM criteria

Results: 30 studies were eligible using 12 different sets of diagnostic criteria for GDM. Ten studies included n > 50, control group, assessment of GDM and BMI. Results were not uniform, but supported that higher BMI, higher age, Asian ethnicity, and fertility treatment increased the risk of GDM in PCOS. In OCC, women with PCOS and controls had similar prevalences of GDM independent of different sets of criteria for GDM.

Conclusion: PCOS may not be an individual risk factor for GDM. Pregnancies in PCOS are characterized by factors known to increase risk of GDM, especially high BMI and fertility treatment.

Keywords
- PCOS
- GDM
- Pregnancy
- Ethnicity
- BMI
1 Introduction

Polycystic ovary syndrome (PCOS) is a frequent endocrine disorder in females with an estimated prevalence of 5 - 10 % [1]. PCOS is usually defined by the Rotterdam criteria, where at least two out of the following criteria must be fulfilled; Clinical and/or biochemical signs of hyperandrogenism, polycystic ovaries and oligo- or anovulation. Additionally, other causes of the symptoms and findings must be ruled out [2]. Insulin resistance is observed in about 50 % of women with PCOS [3] and the risk of type 2 diabetes mellitus (T2D) is reportedly fourfold higher in non-pregnant women with PCOS than those without PCOS, with diagnosis 4 years earlier [4]. Insulin resistance and risk of T2D in PCOS are closely associated with obesity [5, 6] and T2D is rarely diagnosed in normal weight women with PCOS [5-7].

To date there is conflicting evidence whether PCOS per se increases the risk of GDM [8, 9] or whether obesity is the key factor. Available studies regarding risk of GDM in PCOS are mainly retrospective [10-15]. Register-based data have demonstrated that the prevalence of GDM is significantly higher in Danish women with PCOS compared to controls (4 vs. 0.6 %, p<0.001) [4]. Such studies may be biased towards higher incidence of GDM in PCOS, as they potentially favor a more severe PCOS phenotype [4] and are subject to surveillance bias. It is estimated that 10 - 50 % of women with GDM develop diabetes during a 5-year interval following delivery [16, 17]. The prevalence of GDM in cohort studies varied widely between 2 and 32 %, depending on the women included, screening procedure, geographic setting and especially applied diagnostic criteria [18-20].

It has been shown that the use of different diagnostic criteria within the same population may identify women with different phenotypes [21] and indicates the necessity of uniform diagnostic criteria for comparison studies [21]. It is not possible to pool data from all populations, as it is well known that ethnicity affects both PCOS phenotype and prevalence of GDM [22-24]. There has been focus on increased risk of GDM in Asia [22-24], but we need more knowledge about PCOS and GDM from areas such as Africa.

The Hyperglycemia and Adverse Outcome (HAPO) study reported that glucose levels during an oral glucose tolerance test (OGTT) in gestational weeks 24 - 28 were linearly associated with perinatal outcomes [25]. New diagnostic GDM criteria were proposed based on the results from the HAPO study [26] and these GDM criteria were endorsed by the World Health Organization (WHO) in 2013 [27]. However, few studies have been published regarding the impact of implementing these criteria in different populations. In Denmark, GDM is diagnosed by a 75 g OGTT at
gestational week 28, performed in women with clinical risk factors and using a diagnostic 2 h threshold of 9.0 mmol/l [28], resulting in a prevalence of 3% [29]. The implementation of WHO GDM criteria [27] is expected to increase the number of women with GDM substantially [30].

In this paper we 1) review previous studies on GDM prevalence in women with PCOS and 2) present new data on GDM applying two different sets of GDM criteria in a large cohort of unselected Danish pregnant women with prospective characterization of PCOS status.

2 Narrative review

PubMed was searched to identify studies in English published between January 2000 and March 2018, that reported prevalence of GDM in women with PCOS. The following search string was used: (“PCOS” OR “polycystic ovary syndrome”) AND (“GDM” OR “gestational diabetes mellitus” OR “diabetes, gestational” OR “diabetes mellitus, type 2”). The inclusion criteria were original data regarding prevalence of GDM (prospective, retrospective, register-based) in women with PCOS.

836 articles were identified by the initial search. 343 review articles were excluded and additionally 463 articles were excluded because of irrelevance. Thirty studies fulfilled inclusion criteria; 10 prospective [31-40] and 20 retrospective studies [4, 10-15, 23, 41-52]. Included studies reported data on 11,263 women with PCOS and 1,389,161 controls. The median number of women with PCOS per study was 375 (Table 1). The origin of the studies was: 12 European [4, 11, 14, 31-33, 35, 37, 39, 41, 44, 46, 49], 8 Asian [12, 15, 40, 42, 43, 47, 51, 52], 7 American [13, 34, 38, 45, 48] and 3 Australian studies [10, 36, 50].

Twelve different sets of diagnostic criteria for GDM were used in the 30 studies (Table S2). The most frequently used criteria were those of the American College of Obstetricians and Gynecologists (ACOG) [53] (n=7) [23, 32, 33, 39, 42, 45, 49], followed by American Diabetes Association (ADA2000) [54] (n=6) [13, 34, 41-43, 52], WHO1999 [55] (n=5) [33, 35, 37, 38, 51], WHO13/International Association of the Diabetes and Pregnancy Study Group (IADPSG) [26, 56] (n=3) [15, 40, 47], Danish criteria (GDM-DK) [18] (n=2) [4, 46] and the Modified IADPSG (n=2) [35, 37]. The following criteria were only applied in one study each: National Diabetes Data Group (NDDG) [57] (n=1) [12] and Australasian Diabetes in Pregnancy Society (ADIPS) [58] (n=1) [50].
Four studies used their own criteria [11, 14, 31, 44], in 2 studies GDM was self-reported [10, 36] and one study did not define GDM criteria [48].

The study aim was to compare the risk of hyperglycemia in pregnancy in PCOS vs. controls. Therefore, we defined clinically relevant criteria for inclusion of studies in a thorough analysis. The studies should include a control group, a substantial number of participants, arbitrarily > 50 women with PCOS, and assessment of both hyperglycemia and BMI during pregnancy. Furthermore, medical treatment with e.g. metformin during pregnancy should be avoided [59]. Ethnicity affects the PCOS phenotype and the risk of GDM [22-24], and therefore studies were divided according to ethnicity of included women.

Five out of 30 studies [23, 32, 35, 37, 39] included no control group and additional seven out of 30 studies [31, 38, 41, 47, 49, 51, 52] included less than 50 women with PCOS. Four studies [4, 12, 14, 45] were register-based and BMI was not reported. The prospective study by Joham et al. [36] was community based and the diagnosis of GDM or T2D was self-reported. Likewise, GDM was self-reported in the retrospective study by Kakoly et al. [10]. Women with PCOS were treated with metformin during pregnancy in two studies by Glueck et al. [34] and Reyes-Munoz et al. [13]. A total of twenty out of 30 studies [4, 10, 12-14, 23, 31, 32, 34-39, 41, 45, 47, 49, 51, 52] were excluded and therefore 10 out of 30 studies [11, 15, 33, 40, 42-44, 46, 48, 50] were eligible for detailed evaluation. Six out of 10 studies [11, 33, 44, 46, 48, 50] were performed in primarily white women and 4 out of 10 papers [15, 40, 42, 43] included women of predominantly Asian origin.

The prevalence of GDM in six studies performed in predominantly white study populations (Table I) varied from 4.9 to 38.5 % in women with PCOS, and from 5 to 17 % in controls. Four out of 6 studies [11, 33, 46, 48] showed significantly higher prevalence of GDM in women with PCOS compared to controls. Three out of these 4 studies [11, 33] found significantly higher BMI in women with PCOS compared to controls (24.6 vs. 23.7 kg/m², 25.6 vs. 23.0 kg/m² and 24.6 vs. 23.6 kg/m² in PCOS vs. controls, p<0.02, p<0.0001 and p<0.05, respectively) and the remaining study [48] found no significant difference in BMI between women with PCOS and controls (25.9 vs. 23.2 kg/m² in PCOS vs. controls, p<0.23). Age at delivery, was significantly lower in two out of six studies [33, 48] in PCOS compared to controls (30 vs. 30.7 years and 33 vs. 35 years in PCOS vs. controls, respectively, p<0.01 and p<0.002). In one out of 6 studies [11] age was higher in women with PCOS compared to controls (30.4 vs. 29.4 years, p<0.05). Women with PCOS and controls had comparable age in 3 out of 6 studies [44, 46, 50] and age in controls was matched to women with PCOS in one paper [50].
GDM prevalence in the 4 studies performed in Asian populations [15, 40, 42, 43] varied from 1.1 to 55.7% in women with PCOS, and from 1.8 to 29.9% in controls. Three out of 4 studies [15, 40, 42] showed significantly higher prevalence of GDM in women with PCOS compared to controls. One of these 3 studies [15] found significantly higher BMI in women with PCOS vs. controls (p<0.001). Two studies [40, 42] reported no significant difference in BMI between PCOS and controls. However, mean BMIs were numerically higher in PCOS (BMI 23.0 vs. 20.0 kg/m² and 26.1 vs. 25.5 kg/m² (p<0.3)). In one out of 4 studies, Han et al. [43] studied the risk of GDM in both lean and obese women and found that the prevalence of GDM was comparable in PCOS vs. controls (27.5 vs. 27.5 kg/m² in obese and 20.5 vs. 20.6 kg/m² in lean women with PCOS vs. controls, respectively). In all 4 studies [15, 40, 42, 43] maternal age was higher in PCOS compared to control women (29.7 vs. 28.6 years (p<0.001), 30.8 vs. 29.1 years, 30.5 vs. 28.9 years (p<0.002) and in the study by Han et al. 31.6 vs. 32.2 years in obese and 31.2 vs. 32.5 years in lean women, respectively p<0.001).

The six studies on white women [11, 33, 44, 46, 48, 50] will be compared with the present prospective study, OCC.

3 Odense Child Cohort

Odense Child Cohort (OCC) is a prospective cohort study. Details regarding design and study cohort have been published recently [60]. All pregnant women between January 2010 until December 2012 were invited to participate. PCOS was defined as self-reported PCOS or hirsutism alone or together with self-reported irregular menstrual cycle. WHO ICD10 diagnostic codes for hirsutism and PCOS were extracted from the Patient Register of the county of Funen (FPAS) in women without returned questionnaires. The study complied with the Helsinki declaration and was approved by the Regional Scientific Ethics Committee for Southern Denmark (project ID S-20090130). All participants gave written informed consent.

A flow chart for women in OCC is presented in Figure 2 and Figure S1. A total of 2,548 women had information regarding PCOS/hirsutism status, 241 (9.5%) women were categorized as PCOS and the remaining 2,307 women were defined as controls. Among women with known PCOS/hirsutism status, 23 (1%) women were diagnosed with GDM early in pregnancy and were excluded in the present paper. This left 2,525 women eligible for 3rd trimester OGTT. Fasting
plasma glucose (FPG) was available in 1,519 (60 %) and 659 (26 %) underwent an OGTT at GA 28-30; 384 due to risk factors and 275 by randomization. The rate of women undergoing OGTT was similar in PCOS vs. controls (32 vs. 25 %, p<0.1). Risk factors for GDM were defined by Danish guidelines for antenatal care [29]; BMI ≥ 27 kg/m², previous GDM, previous delivery of a macrosomic child (birth weight ≥ 4,500 g), family history of diabetes mellitus (DM) or glucosuria detected during pregnancy.

Women with risk factors for GDM were offered a diagnostic OGTT at gestational age (GA) 28-30 weeks. For each women who was offered OGTT by indication, one random woman from the cohort was offered a diagnostic OGTT at GA 28 weeks matched by gestational age. Randomization of women without risk factors for GDM was conducted consecutively throughout the study period.

As per protocol in the OCC study, venous samples were obtained after overnight fasting and additionally at 1 h and 2 h during a 75 g glucose OGTT. According to WHO13/IADPSG criteria [26, 56], GDM was diagnosed by FPG ≥ 5.1 mmol/l, and/or 1 h plasma glucose (PG) ≥ 10 mmol/l, and/or 2 h PG ≥ 8.5 mmol/l. In the Danish guidelines for antenatal care, GDM was defined by 2 h PG ≥ 9.0 mmol/l [29] and only these women received treatment for GDM.

4 Statistics

Differences between groups were analysed using t-tests for normally distributed continuous variables, Wilcoxon’s rank sum test for non-normally distributed continuous variables and the Chi² test for dichotomous variables. Data are presented as frequency and percentage or median and quartiles. The frequency of GDM was computed after application of diagnostic criteria as described above. A p-value < 0.05 was considered statistically significant. Statistical calculations were performed using Stata version 15.0 (StataCorp, Texas, USA).

5 Results

Baseline characteristics are shown in Table 2. Women with PCOS had significantly higher BMI than women without PCOS (p<0.02), but were of similar age. Women in OCC were younger than the Danish background population (p<0.001) and had slightly higher BMI (p<0.04). Women with PCOS had more pregnancies achieved by fertility treatment and fewer pregnancies achieved within 6 months than controls. Furthermore, by definition, women with PCOS had higher prevalence of irregular menstrual cycle before pregnancy.
The prevalence of GDM applying the two sets of criteria is shown in Figure 2. The prevalence of GDM among women undergoing routine OGTT due to risk factors and randomly selected women were 7.6 and 3.3 %, respectively, using GDM-DK criteria [18]. GDM prevalence based on the WHO13/IADPSG [26, 56] was 64.6 and 40.0 % in women with GDM risk factors and randomly selected women, respectively. GDM diagnosis based on diagnostic venous plasma glucose thresholds at 0 h, 1 h and 2 h during OGTT are presented in Table 3.

The characteristics of women with PCOS and controls diagnosed with GDM according to two different sets of criteria are shown in Table S1. Among women with GDM WHO13/IADPSG criteria [26], we found that fewer women were Caucasian among women with PCOS compared to women without PCOS (90 vs. 94 %, p<0.02). There was no difference in maternal age, BMI or venous plasma glucose in the fasting state or post load (1 h or 2 h) in women with PCOS vs. controls using either sets of criteria.

6 Discussion

6.1 GDM in women with and without PCOS

In this narrative review on hyperglycemia during pregnancy in women with PCOS, 30 studies were identified between 2000-2018. Ten studies were available for detailed review as they included relevant information on a control group, more than 50 participants with PCOS, recorded BMI data and lack of medication for PCOS in pregnancy [11, 15, 33, 40, 42-44, 46, 48, 50]. Six studies included predominantly white women [11, 33, 44, 46, 48, 50] and four studies included women of Asian origin [15, 40, 42, 43]. In the Danish prospective study, OCC, we found similar prevalences of GDM in women with PCOS and controls, irrespective of the diagnostic criteria applied, even though mean BMI was significantly higher in women with PCOS vs. controls (25.3 vs. 24.2 kg/m², p<0.05). Importantly, the inclusion and management of women during pregnancy, regarding indication for OGTT and applied GDM criteria were similar in women with PCOS and controls in OCC and PCOS status was not associated with additional visits or surveillance during pregnancy [61]. Women in OCC were predominantly white and therefore our study results were compared to the 6 studies in predominantly white women [11, 33, 44, 46, 48, 50]. These 6 papers consisted of one recent prospective study [33] and 5 retrospective studies [11, 44, 46, 48, 50]. Relatively few women with PCOS were included in four of the five retrospective studies [11, 44, 48, 50] (n=66,
99, 71 and 60, respectively), whereas the last retrospective study [46] included 199 women with PCOS.

Two studies of white women by Haakova et al. [44] and Vollenhoven et al. [50] reported a similar frequency of GDM in women with PCOS compared to controls (GDM prevalences 4.9 vs. 12.2 % and 22 vs. 17 %, respectively, p>0.05), in accordance with OCC. Importantly, both these studies [44, 50] matched women with PCOS and controls according to age and BMI. Vollenhoven et al. [50] also matched women according to ethnicity. In contrast, 4 out of 6 studies previous studies [11, 33, 46, 48] from white populations reported increased risk of GDM in PCOS vs. controls. The prospective study by de Wilde et al. [33] reported a fourfold increased prevalence of GDM in women with PCOS compared to controls (prevalence GDM in PCOS vs. controls 23 vs. 5 %, p<0.001). However, this study included only with PCOS who required fertility treatment. Further, difference the screening protocol and criteria for GDM differed between PCOS women and controls and BMI was significantly higher in women with PCOS vs. controls (median 24.6 vs. 23.7 kg/m², p<0.02). These factors could explain the increased risk of GDM in PCOS [33]. Mikola et al. [11] and Sterling et al. [48] found 2.2 to 3.2 fold increased risk of GDM in PCOS. Women with PCOS had higher BMI than controls in both studies [11, 48], but the increased risk for GDM in PCOS persisted after correcting for BMI. However, women with PCOS (28, 22) had required fertility treatment, which suggests a more severe PCOS phenotype and in vitro fertilization as well as assisted reproduction are associated with an increased risk of GDM [62]. Women with PCOS tended to be older than controls in the study by Mikola et al. [11] (30.4 vs. 29.5 years, p=0.05), which could also have increased GDM risk [22]. In the study by Sterling et al. [48] women with PCOS were significantly younger than controls (33 vs. 35 years, p<0.002). However, no GDM criteria were cited in this paper [48]. Finally, Mumm et al. [46] reported a significantly higher prevalence of GDM in women with PCOS vs. controls (38.5 vs. 13.8 %, p<0.05). BMI was significantly higher in PCOS compared to controls (p<0.05). PCOS women were recruited from the outpatient clinic and may represent more severe cases of PCOS. Mumm et al. [46] had no data on regional fat mass in their retrospective study, but suggested that central obesity could be an independent predictor of the risk of GDM in women with PCOS [46]. It has been reported, that body composition in women with PCOS and previous GDM is characterized by central fat distribution while BMI was comparable in PCOS and controls [63].

In conclusion, OCC and two previous studies in white women with PCOS [44, 50] reported no increased risk of GDM in PCOS, whereas four [11, 33, 46, 48] studies reported increased
prevalence of GDM. The four contrary studies were heterogeneous in design and study population, making firm conclusions difficult. However, higher BMI, and requirement for fertility treatment could have resulted in hyperglycemia in pregnancy in PCOS, and especially lack of [33] or unreported [48] uniform GDM criteria also limits comparisons.

Four of 10 studies [15, 40, 42, 43] were carried out in Asian women; one prospective [40] and 3 retrospective studies [15, 42, 43], including one study from western Asia, Iran [42]. Three out of 4 studies [15, 40, 42] showed significantly higher prevalence of GDM in women with PCOS compared to controls and one study [43] only found this association in obese women. Just one retrospective study [15] observed significant higher BMI in PCOS vs. controls. Two out of 4 studies [42, 43] included exclusively women with a history of infertility. It has been shown that Asian women with PCOS have an OR of 3.5 for GDM compared to white women [23]. However, use of a standard OGTT may be questioned in an Asian study population as Olabi et al. [24] reported height to be inversely associated with 2 h glucose. Therefore, populations with a lower height, i.e. Asians may receive a relatively higher glucose load which could lead to over-diagnosis of GDM. In the prospective study by Wang et al. [40] the difference in GDM prevalence between lean women with and without PCOS was as high as 38.5 % with an OR of 5.6 in PCOS vs. controls, however, average BMI in lean women were not presented. The GDM prevalence was comparable between obese women with PCOS and controls [40]. Two retrospective studies in Chinese study populations [15, 43] reported a moderately increased risk of GDM in PCOS. Both studies [15, 43] were based on hospital records. However, the selection of women for GDM screening was not described in the study by Xiao et al. [15]. The study by Han et al. [43] only included infertile women and presented data for lean women with PCOS vs. controls (average BMI 20.5 kg/m^2 in PCOS and 20.6 kg/m^2 in controls). The prevalence of GDM was 1.1 % in PCOS and 1.8 % in controls, whereas corresponding prevalence of GDM in obese women was 10.5 and 8.6 %, respectively [40]. In all 4 Asian studies [15, 40, 42, 43] women with PCOS were significantly older than controls, which might partly explain increased GDM prevalence, as previously described [22].

In conclusion, 3 out of the 4 Asian studies [15, 40, 42] showed significantly higher GDM prevalence in women with PCOS compared to controls in lean populations. The last study [43] found only increased GDM prevalence in obese women with PCOS. This study included only infertile women [43]. BMI in 3 of the 4 Asian studies [40, 42, 43] was comparable in women with PCOS vs. controls, but age was significantly higher in women with PCOS in all 4 studies [15, 40,
42, 43]. These findings may suggest that BMI in Asian women is not as important for the risk of GDM in women with PCOS compared to the white populations, however, older age predictably increased the risk of GDM. These data were in accordance with previous papers [22-24].

The present review and results from OCC corroborate findings from a meta-analysis concluding that higher risk of GDM in women with PCOS was a questionable finding because of significant heterogeneity between available studies [8]. However, a recent meta-analysis including 40 studies showed an increased risk of GDM in women with PCOS with a RR of 2.78, but substantial heterogeneity was observed (p<0.001) and subgroup analysis suggested that different study designs and pre-pregnancy BMI might affect these associations [9]. Overall, we consider that past and current data do not support an increased risk of GDM in women with PCOS per se. However, many characteristics in PCOS may elevate risk of hyperglycemia in pregnancy, such as higher BMI, age and fertility treatment. Ethnicity also needs to be considered. Last but not least, in general, the criteria used for diagnosing GDM when comparing PCOS to controls need to be uniformly applied.

6.2 GDM rates for different diagnostic criteria

Depending on diagnostic thresholds for fasting and postload glucose levels, different phenotypes may be identified as having GDM [21]. An overview of different GDM criteria is given in Table S2. The 30 included studies in Table 1 used 12 different sets of diagnostic criteria for GDM. Two out of 30 studies [10, 36] used self-reported GDM based on questionnaires. Fasting and 2 h glucose thresholds values varied from 4.8 to 7.0 mmol/l and 8.0 to 12.2 mmol/l, respectively. In a post-hoc analysis on 273 pregnant women with PCOS, Helseth et al. [35] applied both WHO13/IADPSG and WHO1999 GDM criteria on their study cohort of women with PCOS and reported a GDM prevalence of 24.2 and 25.6 %, respectively. Even though GDM rates were similar, less than one-third of women with GDM by one of the two sets of criteria fulfilled both criteria. Furthermore, the two groups had different profiles for clinical risk factors and thus different in phenotypic characteristics. The study included no control group. In another Norwegian study (n=759), Jenum et al. [64] found WHO13/IADPSG GDM rates of 13.0 % and WHO1999 rates of 31.5 %. These findings indicate that using different GDM criteria might have different impacts in different groups (e.g. PCOS vs. the general population). When testing for GDM in early pregnancy (n=228), Odsæter et al. found a GDM prevalence of 15.5 and 24.1 % by WHO13/IADPSG criteria
(modified as 1 h glucose values were not available) and WHO1999 criteria, respectively. Recently, it has been questioned whether WHO13/IADPSG criteria can be used in early pregnancy, and the IADPSG is no longer recommending this [65]. The HAPO study with 23,957 participants in 15 different centers, found a prevalence of GDM using the WHO13/IADPSG criteria of 17.8 % (9.3 - 25.5 %), with FPG as the diagnostic value in 55 % [66]. The studies in Table 1 with the most substantial increase in GDM prevalence in women with PCOS compared to control, was mainly using the ACOG, ADA [13, 41] and IADPSG [40, 47] criteria with a low FPG thresholds of 5.3 and 5.1 mmol/l, respectively. In addition, one study used local criteria [11] with an even lower FPG at 4.8 mmol/l. Thus, the choice of GDM definition potentially has a major influence on the findings of an association between PCOS and GDM.

In OCC, women with clinical risk factors had a 64.6 % risk for GDM by WHO13/IADPSG criteria compared to a 40.0 % risk in women without risk factors. Corresponding figures for GDM-DK criteria were 7.6 and 3.3 %. Thus, applying WHO13/IADPSG criteria, substantially increased the incidence of GDM compared to the GDM-DK criteria in both women with and without PCOS. The WHO13/IADPSG criteria have been endorsed by the Danish Society of Obstetrics and Gynaecology (DSOG) but implementation is awaiting more data in the Danish population and estimates of health economics [28].

Among the women who underwent OGTT, we found that FPG, 1 h PG and 2 h PG alone identified 42, 13 and 11 % GDM cases, respectively. Figures were similar in women with and without PCOS (Table 3). This is in accordance with the HAPO study where the majority of women with GDM were identified by FPG [66].

6.3 Strengths and limitations in OCC

The main strengths of OCC are the prospective study design with thorough and homogeneous data collection in all women with or without PCOS. The inclusion and management of women during pregnancy, regarding indication for OGTT and applied GDM criteria were similar in women with and without PCOS. Furthermore, women with GDM in early pregnancy were excluded. Women in OCC with PCOS did not have more visits or focus dependent on PCOS status [61]. A limitation was the use of self-reported data on hirsutism, family history of diabetes mellitus, as well as PCOS diagnosis. Nevertheless, the prevalence in this cohort reflected previous estimates in PCOS [67] and self-reported PCOS has been reported to correspond well to the clinical diagnosis [36, 68].
Furthermore, the PCOS diagnosis was validated by extraction of the PCOS diagnosis from the Patient Register.

7 Conclusion

This review revealed that the risk of GDM in white women with PCOS and controls was dependent on the women’s BMI, use of fertility treatment, as well as various GDM criteria. Ethnicity affects the rate of PCOS and GDM. Among Asian women with PCOS and controls, the risk of GDM was dependent of the women’s age and use of fertility treatment.

In the prospective cohort, OCC, the rate of GDM was comparable in women with PCOS compared to controls despite higher BMI in PCOS, suggesting that PCOS per se did not predispose to hyperglycemia in pregnancy. Application of the WHO13/IADPSG criteria for GDM in Danish women with risk factors for GDM would increase the number of GDM cases in the OCC nearly tenfold [41].

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51. Wan HL, Hui PW, Li HW, Ng EH. Obstetric outcomes in women with polycystic ovary syndrome and isolated polycystic ovaries undergoing in vitro fertilization: a retrospective cohort analysis. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obst* 2015; 28: 475-8.


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Legends to figures

*Figure 1.*
Flowchart, narrative review.

*Figure 2.*
Flowchart OCC.
GDM risk divided by OGTT by risk factor and randomization.
Figure 1.
Figure 2.
Legends to tables

Table 1.
Characteristics of studies included in the review.
Data are presented as mean or numbers (percent). NA=not applicable.
\#median, $\$\$non-insulin resistant, *Compared to controls.

Table 2.
Baseline characteristics of 237 women with PCOS and 2,288 controls after exclusion of 23 women with early GDM.
Data are extracted from medical records and presented as number (percent), median (quartiles) and mean (± SD). Data marked with * were based on returned questionnaires (n = 174 women with PCOS and n = 1,361 controls). BMI: Body mass index, DM: diabetes mellitus.
*p<0.05 (PCOS vs. controls).
**p<0.05 (OCC vs. Danish background population).
‡Characteristics in 389,609 Danish women (after exclusion of 2.2% (n=9,014) with GDM) giving birth to a singleton from 2004 to 2010 (mean (± SD)).
Background data are given as mean (± SD) and percent as in the reference.
Available.

Table 3.
Diagnostic criteria for GDM in the fasting state and during OGTT in women with PCOS vs. controls.
Data are presented as numbers (percent).

Table S1.
Maternal characteristics and OGTT results for women with PCOS and controls, according to two different sets of criteria for GDM.
Data are presented as median (25th-75th percentile) or numbers (percent). WHO2013/IADPSG:
Fasting venous plasma glucose ≥ 5.1 mmol/l and/or ≥ 10.0 mmol/l at 1 h and/or ≥ 8.5 mmol/l at 2 h. GDM-DKplasma: 2 h venous plasma glucose ≥ 9.0 mmol/l.
P-value < 0.05 in bold, when comparing characteristics by PCOS status, Wilcoxon’s rank sum test (non-normally distributed variables) and Chi squared test for categorical variables.

Table S2.
Diagnostic threshold values for different GDM criteria.
FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NDDG, National Diabetes Data group; ACOG, American College of Obstetricians and Gynecologists; ADA, American Diabetes Association; WHO, World Health Organization; IADPSG, International Association of Diabetes in Pregnancy Study Group; Mod. IADPSG, modified IADPSG; GDM-DK, Danish national criteria; ADIPS, Australasian Diabetes in Pregnancy Society.
Table 1.

<table>
<thead>
<tr>
<th>Study [reference]</th>
<th>Published</th>
<th>Nationality</th>
<th>Study design</th>
<th>PCOS diagnosis</th>
<th>GDM criteria</th>
<th>GA at OGTT (weeks)</th>
<th>n</th>
<th>Age, mean</th>
<th>BMI, mean</th>
<th>BMI (%)</th>
<th>OGTT performed (%)</th>
<th>Prevalence GDM (%)</th>
<th>Increased risk of GDM in %</th>
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<td>Palm et al. [22]</td>
<td>2018</td>
<td>Denmark</td>
<td>Prospective</td>
<td>ICD-10</td>
<td>GDM-DK</td>
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<td>The Netherlands</td>
<td>Prospective</td>
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<td>ADHD</td>
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<td>Chile</td>
<td>Prospective</td>
<td>SNIH/Rotterdam</td>
<td>WHO</td>
<td>10-16 and 22-28</td>
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<td>51</td>
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<td>29.0%</td>
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<td>24.8%</td>
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<td>IADPSG</td>
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<td>ACOG</td>
<td>ADA</td>
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<td>ADA</td>
<td>24-28</td>
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<td>Czech</td>
<td>Retrospective</td>
<td>Own criteria</td>
<td>Own criteria</td>
<td>second and third</td>
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<td>66</td>
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<td>29.8</td>
<td>23.7</td>
<td>23.2</td>
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<td>Norway</td>
<td>Retrospective</td>
<td>Own criteria</td>
<td>Own criteria</td>
<td>second and third</td>
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<td>355</td>
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<td>32.7</td>
<td>25.2</td>
<td>21.9</td>
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<td>Finland</td>
<td>Retrospective</td>
<td>Own criteria</td>
<td>Own criteria</td>
<td>second and third</td>
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Legend:
- GDM: Gestational Diabetes Mellitus
- PCOS: Polycystic Ovary Syndrome
- GA: Gestational Age
- BMI: Body Mass Index
- OGTT: Oral Glucose Tolerance Test
- WHO: World Health Organization
- ADA: American Diabetes Association
- IADPSG: International Association of Diabetes and Pregnancy Study Groups
- PCOS: Polycystic Ovary Syndrome
- NA: Not Available
- %: Percentage
Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>PCOS</th>
<th>Controls</th>
<th>Danish background population</th>
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<td>$n = 237$</td>
<td>$n = 2,288$</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>30 (27-33)</td>
<td>30 (28-33)</td>
<td>30 (27-33)</td>
<td>-</td>
</tr>
<tr>
<td>Age, years, mean (± SD)**</td>
<td>30.2 (± 4.5)</td>
<td>30.6 (± 4.4)</td>
<td>30.2 (± 4.5)</td>
<td>30.7 (± 4.8)</td>
</tr>
<tr>
<td>Primiparity</td>
<td>1400 (56)</td>
<td>126 (53)</td>
<td>1274 (56)</td>
<td>44.1</td>
</tr>
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<td>BMI, kg/m²*</td>
<td>23.3 (21.2-26.4)</td>
<td>23.8 (21.5-28.0)</td>
<td>23.3 (21.2-26.2)</td>
<td>-</td>
</tr>
<tr>
<td>BMI, kg/m², mean (± SD)**</td>
<td>24.3 (± 4.7)</td>
<td>25.3 (± 5.5)</td>
<td>24.2 (± 4.6)</td>
<td>24.1 (± 4.8)</td>
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<tr>
<td>Caucasian#</td>
<td>2,292 (91)</td>
<td>209 (89)</td>
<td>2,083 (91)</td>
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<tr>
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<td>34 (17)</td>
<td>160 (10)</td>
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<tr>
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<td>13 (12-14)</td>
<td>13 (12-14)</td>
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<td>133 (91)</td>
<td>1,118 (92)</td>
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<td>49 (36)</td>
<td>117 (10)</td>
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<td>51 (36)</td>
<td>592 (50)</td>
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<td>Previous miscarriage#*</td>
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<td>41 (43)</td>
<td>243 (32)</td>
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<tr>
<td>Smoking before pregnancy#</td>
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<td>35 (24)</td>
<td>326 (28)</td>
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<tr>
<td>Smoking during 1st trimester#</td>
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<td>5 (5)</td>
<td>49 (7)</td>
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Table 3.

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<td>68/148 (46)</td>
<td>567/1,371 (41)</td>
</tr>
<tr>
<td>(n=1,519)</td>
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<td>1-hour plasma glucose ≥ 10.0 mmol/l</td>
<td>82/621 (13)</td>
<td>11/75 (15)</td>
<td>71/546 (13)</td>
</tr>
<tr>
<td>(n=621)</td>
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<td></td>
</tr>
<tr>
<td>2-hour plasma glucose ≥ 8.5 mmol/l</td>
<td>66/624 (11)</td>
<td>5/75 (7)</td>
<td>61/549 (11)</td>
</tr>
<tr>
<td>(n=624)</td>
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</table>