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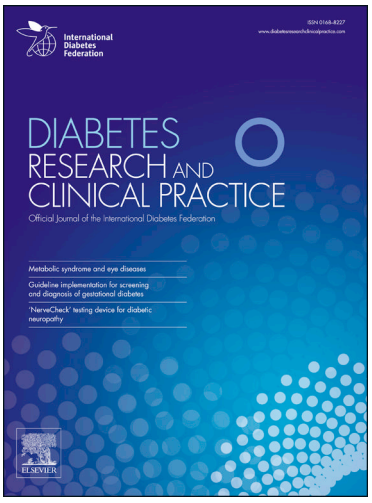

Invited review

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

Camilla Viola Buskbjerg Palm, Dorte Glintborg, Henriette Boye Kyhl, H. David McIntyre, Richard Christian Jensen, Tina Kold Jensen, Dorte Møller Jensen, Marianne Andersen

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Polycystic ovary syndrome and hyperglycaemia in pregnancy.

A narrative review and results from a prospective Danish cohort study.

Authors

Camilla Viola Buskbjerg Palm, MD [1) 4)]
Dorte Glintborg, MD, DMSci, PhD [1)]
Henriette Boye Kyhl, MSC [2) 3)]
H. David McIntyre, MD, FRACP [5) 6)]
Richard Christian Jensen, MD [1)]
Tina Kold Jensen, MD, PhD [3)]
Dorte Møller Jensen, MD, PhD [1) 4)]
Marianne Andersen, MD, DMSci, PhD [1)]

1) Department of Endocrinology and Metabolism, Odense University Hospital, Odense, Denmark
2) Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark
3) Odense Patient Data Exploratory Network (OPEN), Odense University Hospital, Odense, Denmark
4) Department of Gynaecology and Obstetrics, Odense University Hospital, Odense, Denmark
5) Mater Research, University of Queensland, Brisbane, Australia
6) Danish Diabetes Academy, Odense University Hospital, Odense, Denmark

Corresponding author

Marianne Andersen, Department of Endocrinology, Odense University Hospital, Sdr. Boulevard 29. DK-5000 Odense C, Denmark.

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 af GDM (prospective, retrospective, registerbased) 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 fullfilled 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 pregancy 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 retrospetive 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 1***) 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/m^2, 25.6 vs. 23.0 kg/m^2 and 24.6 vs. 23.6 kg/m^2 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/m^2 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 diffence in BMI between PCOS and controls. However, mean BMIs were numerically higher in PCOS (BMI 23.0 vs. 20.0 kg/m^2 and 26.1 vs. 25.5 kg/m^2 ($p<0.3$)). 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/m^2 in obese and 20.5 vs. 20.6 kg/m^2 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/hirsuitism 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/m^2, 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 continous variables, Wilcoxon's rank sum test for non-normally distributed continous variables and the Chi^2 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. Futhermore, 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 on 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/m^2, $p<0.05$). 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 asssociated with additional visits or surveillance during pregnancy [61]. Women in OCC were predominanly white and therefore our study results were compared to the 6 pstudies 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 acccording 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 *deWilde 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/m^2, $p<0.02$). 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 predicatably 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. H*owever, 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), *Odsaeter 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. Futhermore, 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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10 References

1. Goodarzi MO, Azziz R. Diagnosis, epidemiology, and genetics of the polycystic ovary syndrome. *Best practice & research Clinical endocrinology & metabolism* 2006; **20**: 193-205.
2. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertility and sterility* 2004; **81**: 19-25.
3. Glintborg D, Henriksen JE, Andersen M et al. Prevalence of endocrine diseases and abnormal glucose tolerance tests in 340 Caucasian premenopausal women with hirsutism as the referral diagnosis. *Fertility and sterility* 2004; **82**: 1570-9.
4. Rubin KH, Glintborg D, Nybo M et al. Development and Risk Factors of Type 2 Diabetes in a Nationwide Population of Women With Polycystic Ovary Syndrome. *The Journal of clinical endocrinology and metabolism* 2017; **102**: 3848-57.
5. Glintborg D. Endocrine and metabolic characteristics in polycystic ovary syndrome. *Danish medical journal* 2016; **63**.
6. Pelanis R, Mellembakken JR, Sundstrom-Poromaa I et al. The prevalence of Type 2 diabetes is not increased in normal-weight women with PCOS. *Human reproduction (Oxford, England)* 2017; **32**: 2279-86.
7. Ollila MM, West S, Keinanen-Kiukaaniemi S et al. Overweight and obese but not normal weight women with PCOS are at increased risk of Type 2 diabetes mellitus-a prospective population-based cohort study. *Human reproduction (Oxford, England)* 2017; **32**: 968.
8. Toulis KA, Goulis DG, Kolibianakis EM et al. Risk of gestational diabetes mellitus in women with polycystic ovary syndrome: a systematic review and a meta-analysis. *Fertility and sterility* 2009; **92**: 667-77.
9. Yu HF, Chen HS, Rao DP, Gong J. Association between polycystic ovary syndrome and the risk of pregnancy complications: A PRISMA-compliant systematic review and meta-analysis. *Medicine* 2016; **95**: e4863.
10. Kakoly NS, Earnest A, Moran LJ et al. Group-based developmental BMI trajectories, polycystic ovary syndrome, and gestational diabetes: a community-based longitudinal study. *BMC medicine* 2017; **15**: 195.
11. Mikola M, Hiilesmaa V, Halttunen M et al. Obstetric outcome in women with polycystic ovarian syndrome. *Human reproduction (Oxford, England)* 2001; **16**: 226-9.
12. Pan ML, Chen LR, Tsao HM, Chen KH. Relationship between Polycystic Ovarian Syndrome and Subsequent Gestational Diabetes Mellitus: A Nationwide Population-Based Study. *PloS one* 2015; **10**: e0140544.
13. Reyes-Munoz E, Castellanos-Barroso G, Ramirez-Eugenio BY et al. The risk of gestational diabetes mellitus among Mexican women with a history of infertility and polycystic ovary syndrome. *Fertility and sterility* 2012; **97**: 1467-71.
14. Roos N, Kieler H, Sahlin L et al. Risk of adverse pregnancy outcomes in women with polycystic ovary syndrome: population based cohort study. *BMJ (Clinical research ed)* 2011; **343**: d6309.
15. Xiao Q, Cui YY, Lu J et al. Risk for Gestational Diabetes Mellitus and Adverse Birth Outcomes in Chinese Women with Polycystic Ovary Syndrome. *International journal of endocrinology* 2016; **2016**: 5787104.
16. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes care* 2002; **25**: 1862-8.

17. Lee AJ, Hiscock RJ, Wein P et al. Gestational diabetes mellitus: clinical predictors and long-term risk of developing type 2 diabetes: a retrospective cohort study using survival analysis. *Diabetes care* 2007; **30**: 878-83.
18. Jensen DM, Damm P, Sorensen B et al. Proposed diagnostic thresholds for gestational diabetes mellitus according to a 75-g oral glucose tolerance test. Maternal and perinatal outcomes in 3260 Danish women. *Diabetic medicine : a journal of the British Diabetic Association* 2003; **20**: 51-7.
19. Prutsky GJ, Domecq JP, Sundaresh V et al. Screening for gestational diabetes: a systematic review and meta-analysis. *The Journal of clinical endocrinology and metabolism* 2013; **98**: 4311-8.
20. Wendland EM, Torloni MR, Falavigna M et al. Gestational diabetes and pregnancy outcomes--a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria. *BMC pregnancy and childbirth* 2012; **12**: 23.
21. Arora GP, Thaman RG, Prasad RB et al. Prevalence and risk factors of gestational diabetes in Punjab, North India: results from a population screening program. *European journal of endocrinology* 2015; **173**: 257-67.
22. Carolan M, Davey MA, Biro MA, Kealy M. Maternal age, ethnicity and gestational diabetes mellitus. *Midwifery* 2012; **28**: 778-83.
23. Lo JC, Yang J, Gunderson EP et al. Risk of Type 2 Diabetes Mellitus following Gestational Diabetes Pregnancy in Women with Polycystic Ovary Syndrome. *Journal of diabetes research* 2017; **2017**: 5250162.
24. Olabi B, Bhopal R. Diagnosis of diabetes using the oral glucose tolerance test. *BMJ (Clinical research ed)* 2009; **339**: b4354.
25. Metzger BE, Lowe LP, Dyer AR et al. Hyperglycemia and adverse pregnancy outcomes. *The New England journal of medicine* 2008; **358**: 1991-2002.
26. Metzger BE, Gabbe SG, Persson B et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes care* 2010; **33**: 676-82.
27. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. *Diabetes research and clinical practice* 2014; **103**: 341-63.
28. DSOG. GDM guideline. 2014 [cited; Available from:
29. Jensen DM, Molsted-Pedersen L, Beck-Nielsen H et al. Screening for gestational diabetes mellitus by a model based on risk indicators: a prospective study. *American journal of obstetrics and gynecology* 2003; **189**: 1383-8.
30. McIntyre HD, Jensen DM, Jensen RC et al. Gestational Diabetes Mellitus: Does One Size Fit All? A Challenge to Uniform Worldwide Diagnostic Thresholds. *Diabetes care* 2018.
31. Bjercke S, Dale PO, Tanbo T et al. Impact of insulin resistance on pregnancy complications and outcome in women with polycystic ovary syndrome. *Gynecologic and obstetric investigation* 2002; **54**: 94-8.
32. de Wilde MA, Goverde AJ, Veltman-Verhulst SM et al. Insulin action in women with polycystic ovary syndrome and its relation to gestational diabetes. *Human reproduction (Oxford, England)* 2015; **30**: 1447-53.
33. de Wilde MA, Lamain-de Ruiter M, Veltman-Verhulst SM et al. Increased rates of complications in singleton pregnancies of women previously diagnosed with polycystic ovary syndrome predominantly in the hyperandrogenic phenotype. *Fertility and sterility* 2017; **108**: 333-40.

34. Glueck CJ, Bornovali S, Pranikoff J et al. Metformin, pre-eclampsia, and pregnancy outcomes in women with polycystic ovary syndrome. *Diabetic medicine : a journal of the British Diabetic Association* 2004; **21**: 829-36.
35. Helseth R, Vanky E, Salvesen O, Carlsen SM. Gestational diabetes mellitus among Norwegian women with polycystic ovary syndrome: prevalence and risk factors according to the WHO and the modified IADPSG criteria. *European journal of endocrinology* 2013; **169**: 65-72.
36. Joham AE, Ranasinha S, Zoungas S et al. Gestational diabetes and type 2 diabetes in reproductive-aged women with polycystic ovary syndrome. *The Journal of clinical endocrinology and metabolism* 2014; **99**: E447-52.
37. Odsaeter IH, Asberg A, Vanky E, Carlsen SM. HbA1c as screening for gestational diabetes mellitus in women with polycystic ovary syndrome. *BMC endocrine disorders* 2015; **15**: 38.
38. Sir-Petermann T, Echiburu B, Maliqueo MM et al. Serum adiponectin and lipid concentrations in pregnant women with polycystic ovary syndrome. *Human reproduction (Oxford, England)* 2007; **22**: 1830-6.
39. Veltman-Verhulst SM, van Haeften TW, Eijkemans MJ et al. Sex hormone-binding globulin concentrations before conception as a predictor for gestational diabetes in women with polycystic ovary syndrome. *Human reproduction (Oxford, England)* 2010; **25**: 3123-8.
40. Wang Y, Zhao X, Zhao H et al. Risks for gestational diabetes mellitus and pregnancy-induced hypertension are increased in polycystic ovary syndrome. *BioMed research international* 2013; **2013**: 182582.
41. Altieri P, Gambineri A, Prontera O et al. Maternal polycystic ovary syndrome may be associated with adverse pregnancy outcomes. *European journal of obstetrics, gynecology, and reproductive biology* 2010; **149**: 31-6.
42. Ashrafi M, Sheikhan F, Arabipoor A et al. Gestational diabetes mellitus risk factors in women with polycystic ovary syndrome (PCOS). *European journal of obstetrics, gynecology, and reproductive biology* 2014; **181**: 195-9.
43. Han AR, Kim HO, Cha SW et al. Adverse pregnancy outcomes with assisted reproductive technology in non-obese women with polycystic ovary syndrome: a case-control study. *Clinical and experimental reproductive medicine* 2011; **38**: 103-8.
44. Haakova L, Cibula D, Rezabek K et al. Pregnancy outcome in women with PCOS and in controls matched by age and weight. *Human reproduction (Oxford, England)* 2003; **18**: 1438-41.
45. Lo JC, Feigenbaum SL, Escobar GJ et al. Increased prevalence of gestational diabetes mellitus among women with diagnosed polycystic ovary syndrome: a population-based study. *Diabetes care* 2006; **29**: 1915-7.
46. Mumm H, Jensen DM, Sorensen JA et al. Hyperandrogenism and phenotypes of polycystic ovary syndrome are not associated with differences in obstetric outcomes. *Acta obstetricia et gynecologica Scandinavica* 2015; **94**: 204-11.
47. Sawada M, Masuyama H, Hayata K et al. Pregnancy complications and glucose intolerance in women with polycystic ovary syndrome. *Endocrine journal* 2015; **62**: 1017-23.
48. Sterling L, Liu J, Okun N et al. Pregnancy outcomes in women with polycystic ovary syndrome undergoing in vitro fertilization. *Fertility and sterility* 2016; **105**: 791-7.e2.
49. Turhan NO, Seckin NC, Aybar F, Inegol I. Assessment of glucose tolerance and pregnancy outcome of polycystic ovary patients. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2003; **81**: 163-8.

50. Vollenhoven B, Clark S, Kovacs G et al. Prevalence of gestational diabetes mellitus in polycystic ovarian syndrome (PCOS) patients pregnant after ovulation induction with gonadotrophins. *The Australian & New Zealand journal of obstetrics & gynaecology* 2000; **40**: 54-8.
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 Obstet* 2015; **28**: 475-8.
52. Weerakiet S, Srisombut C, Rojanasakul A et al. Prevalence of gestational diabetes mellitus and pregnancy outcomes in Asian women with polycystic ovary syndrome. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2004; **19**: 134-40.
53. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *American journal of obstetrics and gynecology* 1982; **144**: 768-73.
54. Gestational diabetes mellitus. *Diabetes care* 2000; **23 Suppl 1**: S77-9.
55. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic medicine : a journal of the British Diabetic Association* 1998; **15**: 539-53.
56. WHO Guidelines Approved by the Guidelines Review Committee. *Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy*. Geneva: World Health Organization
Copyright (c) World Health Organization 2013. 2013.
57. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. *Diabetes* 1979; **28**: 1039-57.
58. Hoffman L, Nolan C, Wilson JD et al. Gestational diabetes mellitus--management guidelines. The Australasian Diabetes in Pregnancy Society. *The Medical journal of Australia* 1998; **169**: 93-7.
59. Pedersen KD, Bulow NS, Aaboe K et al. [Metformin and the obstetric patient]. *Ugeskrift for laeger* 2015; **177**: V05150438.
60. Finnbogadottir SK, Glintborg D, Jensen TK et al. Insulin resistance in pregnant women with and without polycystic ovary syndrome, and measures of body composition in offspring at birth and three years of age. *Acta obstetricia et gynecologica Scandinavica* 2017; **96**: 1307-14.
61. Kyhl HB, Jensen TK, Barington T et al. The Odense Child Cohort: aims, design, and cohort profile. *Paediatric and perinatal epidemiology* 2015; **29**: 250-8.
62. Jones BJ, Zollner J, Haynes S et al. In vitro fertilization treatment influences glucose tolerance in multiple pregnancy. *Diabetic medicine : a journal of the British Diabetic Association* 2013; **30**: 252-4.
63. Thomann R, Rossinelli N, Keller U et al. Differences in low-grade chronic inflammation and insulin resistance in women with previous gestational diabetes mellitus and women with polycystic ovary syndrome. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2008; **24**: 199-206.
64. Jenum AK, Morkrid K, Sletner L et al. Impact of ethnicity on gestational diabetes identified with the WHO and the modified International Association of Diabetes and Pregnancy Study Groups criteria: a population-based cohort study. *European journal of endocrinology* 2012; **166**: 317-24.

65. McIntyre HD, Sacks DA, Barbour LA et al. Issues With the Diagnosis and Classification of Hyperglycemia in Early Pregnancy. *Diabetes care* 2016; **39**: 53-4.
66. Sacks DA, Hadden DR, Maresh M et al. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Diabetes care* 2012; **35**: 526-8.
67. Azziz R, Woods KS, Reyna R et al. The prevalence and features of the polycystic ovary syndrome in an unselected population. *The Journal of clinical endocrinology and metabolism* 2004; **89**: 2745-9.
68. Taponen S, Martikainen H, Jarvelin MR et al. Hormonal profile of women with self-reported symptoms of oligomenorrhea and/or hirsutism: Northern Finland birth cohort 1966 study. *The Journal of clinical endocrinology and metabolism* 2003; **88**: 141-7.

Legends to figures

Figure 1.
Flowchart, narrative review.

Figure 2.
Flowchart OCC.
GDM risk divided by OGTT by risk factor and randomization.

Figure 1.

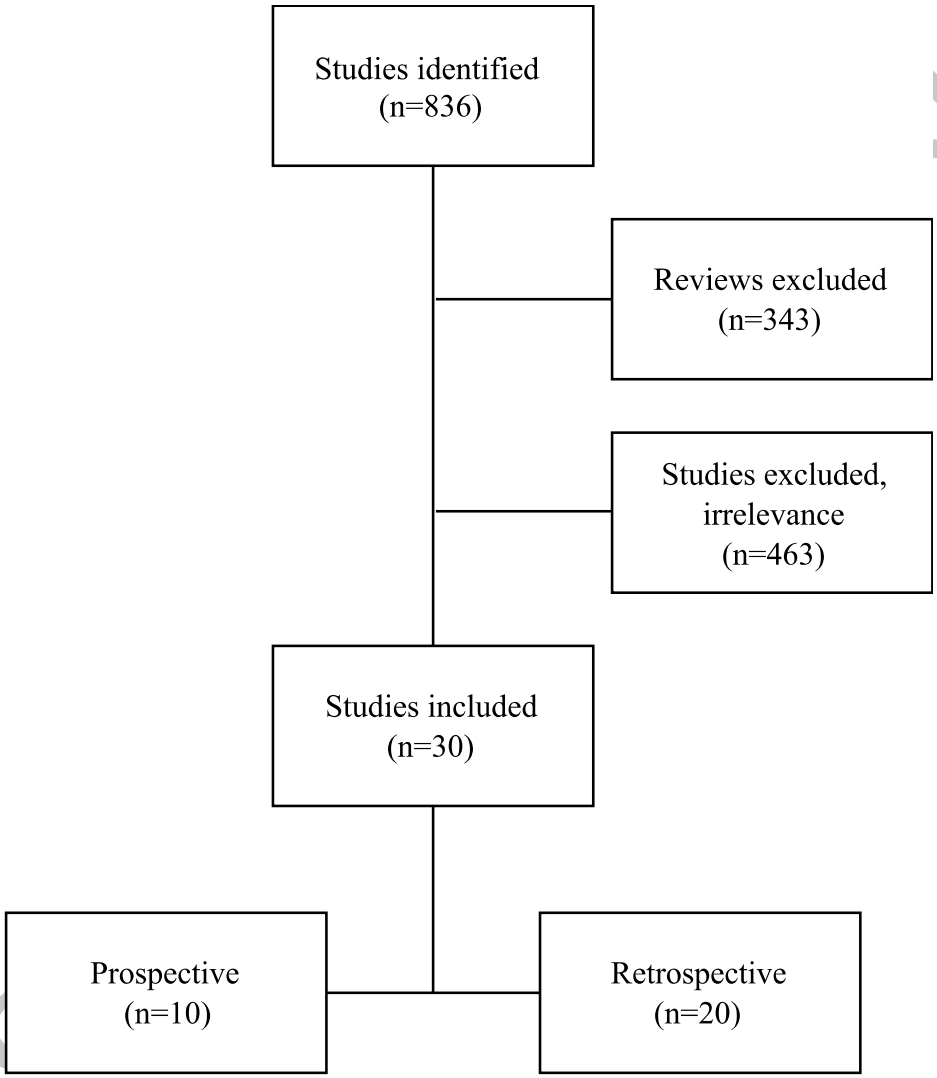
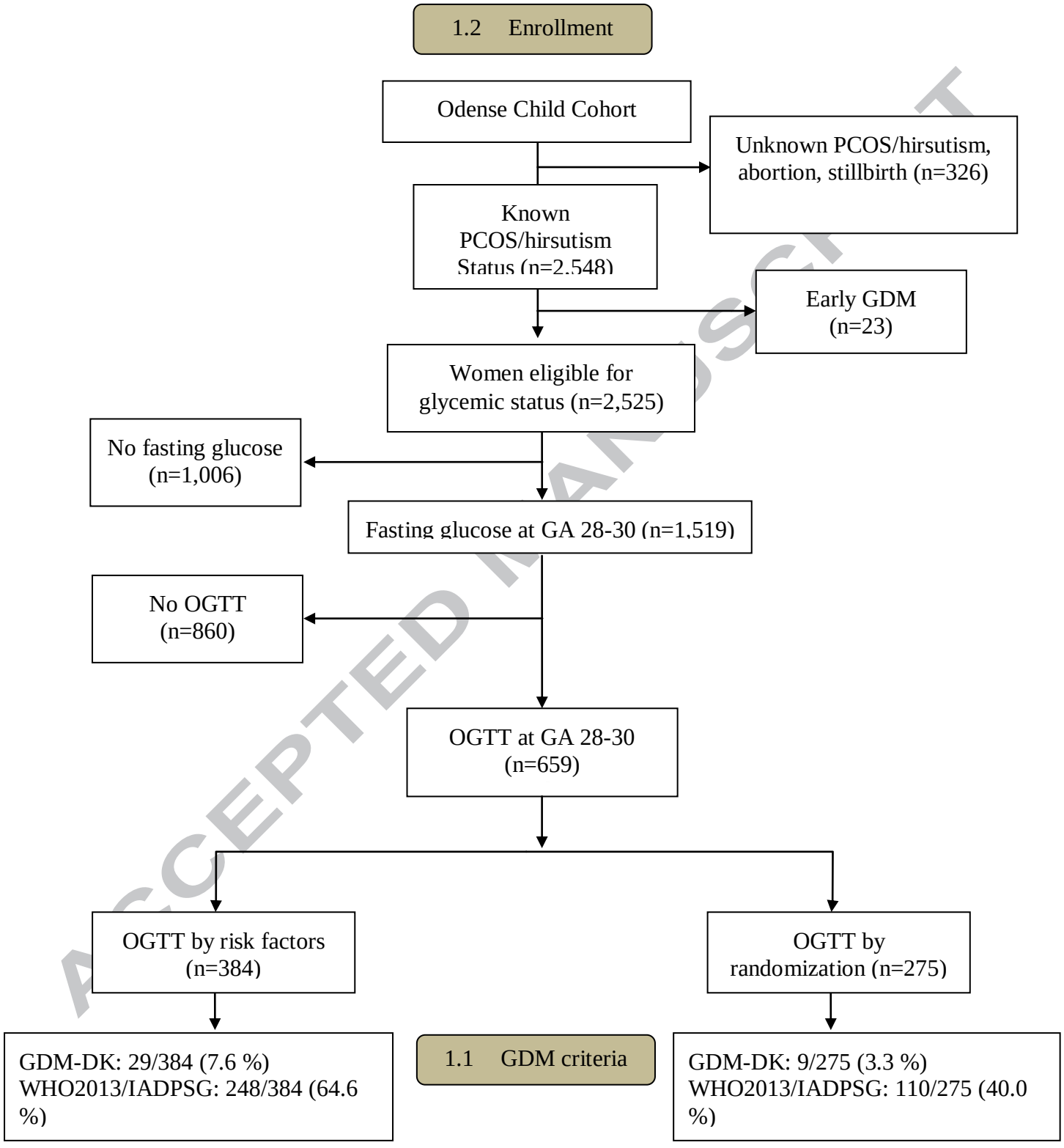


Figure 2.



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 (25^{th}-75^{th} 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.

Study (reference)	Published	Nationality	Study design	PCOS diagnosis	GDM criteria	GA at OGTT (weeks)	n		Age, mean		BMI, mean		BMI (%)						OGTT performed (%)		Prevalence GDM (%)		Increased risk of GDM in
													PCOS			controls							
							PCOS	controls	PCOS	controls	PCOS	controls	≤24.9	25.0-29.9	≥30.0	≤24.9	25.0-29.9	≥30.0	PCOS	controls	PCOS	controls	
				Selfreported and	WHO13/IADPSG																53	54	No
Palm et al.	2018	Denmark	Prospective	ICD-10	GDM-DK	28-30	237	2,288	30.6	30.2	25.3	24.2	60.3	20.3	19.4	66.9	22.9	10.2	32	25	5	6	No
Lo et al. [23]	2017	California	Retrospective	Rotterdam	ACOG	NA	988	NA	32.9	NA	NA		19.3	25.5	55.3		NA			NA	19.8	NA	NA
Rubin et al. [4]	2017	Denmark	Retrospective	ICD-10	GDM-DK	28-30	1,162	54,680	NA		NA		40	25	35		NA			NA	4	0.6	Yes
deWilde et al. [33]	2017	The Netherlands	Prospective	Rotterdam	ACOG/WHO	24-26	188	2,889	30.0#	30.7#	24.6#	23.7#		NA			NA		100	Risk factors	23	5	Yes
Kakoly et al. [10]	2017	Australia	Retrospective	Selfreported	Selfreported	NA	662	7,326	36.6	36.8	29.2	26.2		NA			NA			NA	14.1	7.4	Yes
Xiao et al. [15]	2016	China	Retrospective	Rotterdam	IADPSG	24-28	352	2,037	27.7	28.6	NA		86.2	12.3	1.5	94.4	5.0	0.6	100	100	18	14	Yes
deWilde et al. [32]	2015	The Netherlands	Prospective	Rotterdam	ACOG	24-26	72	NA	29.6#	NA	24.4#	NA		NA			NA		100	n/a	31	NA	NA
					WHO																24.1		
Odsæter et al. [37]	2015	Norway	Prospective	Rotterdam	Mod.IADPSG	first trimester	228	NA	30#	NA	27.3#	NA		NA			NA		100	n/a	15.5	NA	NA
Pan et al. [12]	2015	Taiwan	Retrospective	ICD-9	NDDG	24-28	3,109	31,090	29.1	29.1	NA			NA			NA		100	100	20	11	Yes
Sawada et al. [47]	2015	Japan	Retrospective	Japanese criteria	IADPSG	NA	49	49	31.7	31.9	24.4	24.2		NA			NA		100	100	24.5	10.2	Yes
Sterling et al. [48]	2015	Canada	Retrospective	Rotterdam	NA	NA	71	323	33#	35#	24.6	23.6		NA			NA			NA	15.5	5	Yes
Joham et al. [36]	2014	Australia	Prospective	Selfreported	Selfreported	NA	478	8,134	30.5	30.6	28.0	25.1	42.2	25.7	32.2	62.6	22.4	15.1		NA	11	4	Yes
Mumm et al. [46]	2014	Denmark	Retrospective	Rotterdam	GDM-DK	28-30	157	995	29#	29#	25.9#	23.2#		NA			NA		20	12	38.5	13.8	Yes
Ashrafi et al. [42]	2014	Iran	Retrospective	Rotterdam	ADA/ACOG	24-28	234	234	29.6	30.7	26.1	25.5		NA			NA			NA	44.4	29.9	Yes
Wan et al. [51]	2014	Hong Kong	Retrospective	Rotterdam	WHO	NA	24	171	31.4	32.7	22.8	21.5		NA			NA			NA	29.2	30.4	No
					WHO																25.6		
Helseth et al. [35]	2013	Norway	Prospective	Rotterdam	Mod. IADPSG	32	273	NA	29.4	n/a	29.0	NA		NA			NA		100	n/a	24.2	NA	NA
Wang et al. [40]	2013	China	Prospective	Rotterdam	IADPSG	24-28	115	592	30.8	29.1	23.0	20.0		NA			NA		100	100	55.7	17.2	Yes
Reyes-Munoz et al. [13]	2012	Mexico	Retrospective	Rotterdam	ADA	14-24 and 24-28	52	52	29.1	29.0	27.5	27.5	19.2	57.6	23	19.2	57.6	23	100	100	26.9	9.6	Yes
Roos et al. [14]	2011	Sweden	Retrospective	ICD-9/ICD-10	Own criteria	NA	379	1,191,336	NA	NA	NA	NA	39.4	28.5	32.1	65.2	24.5	10.3		NA	3	1	Yes
									31.6	32.2	27.5	27.5									10.5	8.6	
Han et al. [43]	2011	Korea	Retrospective	Rotterdam	ADA	24	336	1,003	31.2	32.5	20.5	20.6		NA			NA			NA	1.1	1.8	No
Veltmann-Verhulst et al. [39]	2010	The Netherlands	Prospective	Rotterdam	ACOG	24-26	50	NA	NA		NA			NA			NA		100	n/a	42	NA	NA
Altieri et al. [41]	2010	Italy	Retrospective	Selfreported	ADA	NA	15	159	34.7	32.6	24.3	23.0	60	40		81.8	18.9			NA	20	4	Yes
Sir-Petermann et al. [38]	2007	Chile	Prospective	NIH/Rotterdam	WHO	10-16 and 22-28	48	51	29.0#	26.0#	28.6#	24.2#		NA			NA		100	100	12.2	2	Yes
Lo et al. [45]	2006	California	Retrospective	ICD-9	ACOG	NA	1,542	84,882	31.4	29.7	NA			NA			NA		95	95	14.3	5.9	Yes
Glueck et al. [34]	2004	USA	Prospective	Rotterdam	ADA	26-28	90	252	33	29	33.8	25.6		NA			n/a			NA	9.5	15.9	No
Weerakiet et al. [52]	2004	Thailand	Retrospective	Rotterdam	ADA	24-28	47	264	31.6	31.3	24.0	22.1	63.8	36.2		85.2	14.8		76.6	37.9	22.2	18	No
Turhan et al. [49]	2003	Turkey	Retrospective	Rotterdam	ACOG	24-28	38	136	27.6	26.6	31.5	23.6		NA			NA		100	100	2.6	8.1	No
Haakova et al. [44]	2003	Czech Republic	Retrospective	Rotterdam	Own criteria	second and third trimester	66	66	29	29.8	23.7	23.2		NA			NA		100	100	4.92	12.2	No
Bjercke et al. [31]	2002	Norway	Prospective	Rotterdam	Own criteria	NA	29$	355	31.5	32.7	25.2	21.9		NA			n/a			NA	7	0.6	Yes
Mikola et al. [11]	2001	Finland	Retrospective	Rotterdam	Own criteria	second trimester	99	737	30.4	29.4	25.6	23.0	n/a	53		n/a	24		32	35	20	9	Yes
Vollenhoven et al. [50]	2000	Australia	Retrospective	Rotterdam	ADIPS	26-28	60	60	NA		27.1	26.5		NA			NA		100	100	22	17	No

Table 2.

	Total	**PCOS**	**Controls**	**Danish background population¤**
	n = 2,525	*n = 237*	*n = 2,288*	
Age, years	30 (27-33)	30 (28-33)	30 (27-33)	-
Age, years, mean (± SD)**	30.2 (± 4.5)	30.6 (± 4.4)	30.2 (± 4.5)	30.7 (± 4.8**)**
Primiparity	1400 (56)	126 (53)	1274 (56)	44.1
BMI, kg/m^2*	23.3 (21.2-26.4)	23.8 (21.5-28.0)	23.3 (21.2-26.2)	-
BMI, kg/m^2, mean (± SD)**	24.3 (± 4.7)	25.3 (± 5.5)	24.2 (± 4.6)	24.1 (± 4.8)
Caucasian#	2,292 (91)	209 (89)	2,083 (91)	-
Family history of DM#*	194 (10)	34 (17)	160 (10)	-
Age at menarche, years#*	13 (12-14)	13 (12-14)	13 (12-14)	-
Previous oral contraceptive pill treatment#	1251 (92)	133 (91)	1,118 (92)	-
Pregnancy achieved by fertility treatment#*	166 (12)	49 (36)	117 (10)	-
Pregnancy achieved within 6 months#	643 (48)	51 (36)	592 (50)	-
Previous pregnancy#	843 (56)	95 (61)	748 (56)	-
Previous miscarriage#*	284 (34)	41 (43)	243 (32)	-
Smoking before pregnancy#	361 (27)	35 (24)	326 (28)	-
Smoking during 1st trimester#	54 (7)	5 (5)	49 (7)	12.6
Regular menstrual cycle before pregnancy#*	1208 (91)	86 (71)	1,122 (93)	-

Table 3.

WHO/IADPSG criteria	**Total**	**PCOS**	**Controls**
Fasting plasma glucose ≥ 5.1 mmol/l (*n=1,519*)	635/1,519 (42)	68/148 (46)	567/1,371 (41)
1-hour plasma glucose ≥ 10.0 mmol/l (*n=621*)	82/621 (13)	11/75 (15)	71/546 (13)
2-hour plasma glucose ≥ 8.5 mmol/l (*n=624*)	66/624 (11)	5/75 (7)	61/549 (11)