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Time to improve the communication of evidence-based medicine to pregnant women: a review of an exemplary framework related to the prevention of gestational diabetes

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Debate

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Abstract

BACKGROUND Medical specialists are frequently challenged to understand and explain the best evidence even when study results are contradictive. During pregnancy, communication of evidence should motivate women to realize life style changes in favor of themselves and their offspring. MAIN BODY On the topic of prevention of gestational diabetes alone, we found 17 systematic reviews/meta-analyses. Outcomes, reporting and methodological quality differed according to PRISMA, ROBIS and AMSTAR tools. CONCLUSIONS We propose a methodology to select and transform the best evidence into a format illustrating benefits and harms of interventions as fact boxes and icon arrays, which may be applied in other fields of obstetrics.

Background

Gestational diabetes mellitus (GDM) is defined as glucose intolerance first diagnosed in pregnancy (1). In 2012, the prevalence of GDM was 17.8% with a range of 9.3–25.5% (2). GDM is associated with elevated risks for pre-eclampsia, perinatal mortality, fetal macrosomia, shoulder dystocia or cesarean delivery. Metzger et al. already reported on abnormal maternal postpartum glucose tolerance requiring early and continuing follow-up of all women with GDM (3). Later in life, increased hyperinsulinemia, dyslipidemia, type–2 diabetes mellitus (DM II), hypertension, and cardiovascular disease (CVD) were described (4). Glucose resistance appears earlier in obese women due to pre-existing impaired insulin resistance. Overweight, obesity and excessive gestational weight gain (EGWG) (5) as explained as a weight gain of > 0.27 kg/week or even > 0.41 kg/week (6) are all associated with increased risks of GDM. An individualized prediction is provided by first trimester algorithms with a sensitivity of up to 80% (7–10) pointing towards pre-existing risk-profiles that lower the threshold for the disease (11–13). The risk to develop overt DM after a pregnancy with GDM increases with age resulting in a cumulative 15 year risk of 25% (14).

Barker et al. postulated that the global incidence of GDM mainly depends on a mismatch between the pre-and postnatal environment (15) determining the increasing prevalence in regions with previously low rates of GDM. There is an U-shaped relation between low (OR 2.15, 95% CI 1.29–3.50) and high BW (OR: 1.97, 95% CI: 1.12–3.45) and subsequent GDM in females (16). Prenatal famine exposure and fetal growth restriction (FGR) were associated with impaired glucose tolerance, proinsulin and insulin secretion in adulthood (17–19), but also fetal macrosomia associated with GDM increases the risk of childhood obesity (20) both as compared to controls. Hypertriglyceridemia was diagnosed in 14/68 children (21%) before puberty (21). At the age of 11 years, the risk for metabolic syndrome was 3.6-fold higher (22). As adults, the risks of insulin resistance and metabolic syndrome (21, 23), CVD, insulin-dependent DM and early mortality (24) are increased. Offspring with FGR of mothers with GDM had also increased risks for metabolic syndrome: aOR 1.29 (95% CI 1.24–1.35) (25).

The rising global rates of overweight, obesity, GDM and type-II diabetes require urgent consideration by policy makers and awareness of physicians and future parents. Therefore, health care providers should

translate the evidence into formats recognizable for lay people. In this perspective, we evaluated current systematic reviews (SRs) and meta-analyses to reduce GDM and present a framework for communication. In other fields of medicine, it has been shown that fact boxes and icon arrays can enable patients without medical or statistical background to make informed decisions (26, 27) by presenting benefits and harms (28–30). It would be ideal if improved health literacy obtained during pregnancy would help mothers to maintain a healthier life style and improve the health of their offspring.

Main Text

Selection of the best evidence

Already the term “systematic review and meta-analysis” seems to suggest a magic “state of the art”. However, SRs and meta-analyses may show contradictive results. This is difficult to understand for clinicians involved in counselling and even more for their patients. Meanwhile, statisticians or researchers produce a flash flood of SRs about clinical procedures which they might have never performed involving randomized controlled trials (RCTs) from health care systems they are not familiar with. Senior clinicians who do not necessarily have the time for research are expected to follow the conclusions although these may differ from their daily good medical practice (GMP). Whether GMP was at all considered within RCTs of SRs is retrospectively difficult to determine and frequently not analyzed. There is a need for transparency how to determine clinical protocols and audit procedures, to select the best evidence, to exclude studies prone for bias and to transform results of RCTs, SRs and meta-analyses of different quality into messages which are of benefit for our patients, e.g. mothers and their offspring.

By performing a literature search up to December 2018 utilizing Medline, Web of Science and the Cochrane Library related to the prevention of GDM and using search terms: pregnancy, overweight, obesity, weight gain, diabetes, GDM, perinatal mortality, systematic reviews and meta-analysis we identified 17 meta-analyses and systematic reviews using GDM as a primary outcome:

- 6/17 investigated only dietary counselling (31–36),
- 4/17 only supervised exercise programs (37–40),
- 7/17 combined dietary and physical exercise interventions (41–47).

All intervention participants had been tested versus groups with standard care. Only 6/17 studies used macrosomia or large for gestational age (LGA) as primary or secondary outcome, 4/17 looked for perinatal mortality (46). In 14/17 publications all maternal BMI categories were considered, 2 SRs exclusively concentrated on pregnant women with overweight and obesity (31, 42), only 1/17 on normal weight women (32). Several RCTs were cited more than once. Therefore, a summary of all SRs would cause a bias. Categorizing investigated lifestyle interventions showed varying results:

- Among 6 SRs investigating only dietary advice only one SR with women and a BMI > 25 kg/m2 reported that the intervention significantly reduced GDM in accordance with a sub-analysis of

women with a BMI >25 kg/m2 within another publication (30). One SR investigating a low-glycemic index diet found a decreased rate of LGA children (36). Other significant outcome variables were a reduction of maternal weight gain (4/6 SRs), of pregnancy-related hypertension (2/5 SRs), fasting and postprandial glucose and post-partum weight retention (both in 1/6 SRs).

- Among 4/17 SRs investigating physical activity and exercise programs during pregnancy 3/4 found a significant reduction of GDM, 2/4 showed a significant reduction of gestational weight gain in mothers stimulated to exercise and 1/4 a significant reduction of LGA infants.
- Among 7/17 SRs investigating counselling of both physical exercise and diets, 2/7 found a significant reduction of GDM when the interventions started early and 4/7 described a significant reduction of maternal weight gain during pregnancy.

To extract the best evidence we analyzed the reporting and methodological quality of the publications using the PRISMA (48), ROBIS (49), AMSTAR–1 (50) and AMSTAR–2 tools (51) to design a fact box with a corresponding icon array to make the information accessible to those who are less familiar with a tabular format. Fact boxes contain a description of the reference class, a comparison of at least two groups, the effects in absolute numbers, and a summary of benefits and harms (52). Their development follows evidence-based medicine according to Sackett et al. (53). Fact boxes may help patients to understand the evidence in case of medical uncertainty independently of the opinion of their health care providers who tend to deny uncertainty, downplay risks and overstate benefits of interventions (54). Several RCTs have shown that fact boxes and icon arrays are effective tools for informing lay people. In addition, they may improve the understanding of statistical data and of benefits and harms by relating the data to a group of 100 or 1000 participants (52). Although we already suggested to use fact boxes, albeit not in combination with icon arrays (55, 56), these tools have not yet been integrated in maternal-fetal medicine.

Within a stepwise evaluation, only 4/17 SRs fulfilled all by PRISMA demanded reporting quality items for registration, study question, literature search, data abstraction, and result evaluation. Only these SRs and meta-analyses are summarized in Table 1 for dietary intervention (35), exercise (38) and the combination of dietary and exercise counselling (44, 47). Using ROBIS criteria all 4 SRs were characterized as “low risk of bias”. None of the SRs explicitly explained why only RCTs were integrated which is 1/16 AMSTAR–2 criteria; thus only 2 SRs received 15/16 “YES” answers by the AMSTAR–2 criteria although 11/11 AMSTAR–1 points (35, 44). From these remaining two SRs we chose the study of Tieu et al. to create a fact box and icon array because it concentrated on only one intervention which facilitated interpretation of the findings for lay people (35).

Figure 1 illustrates that dietary counselling in pregnant women had no significant impact on the prevention of GDM, although there was a trend to reduce GDM based on low quality studies. However, about 10/100 pregnant women without, but only 3/100 women with nutritional counselling developed high blood pressure which means that in about 7/100 women hypertensive disorders in pregnancy (HDP) could be prevented. When the exact numbers of two groups differ, non-significant differences can appear

as relevant group differences. Contrary to previous papers, we therefore now present the absolute number of the control group instead of the lowest number.

Specific interventions

The fact box shows that dietary counselling did not increase risks but reduced HDP (Figure 1). This general information can be expanded by details from singular RCTs:

Dietary counselling

The components of women's diets influence GDM risks (57). Consumption of sugar-sweetened drinks, potatoes (58), animal fat and cholesterol (59), high glycemic load and low-cereal fiber diets (60) are associated with a risk of GDM. Alternatively, a high-fiber diet (60), intake of vegetables, a substitution of red meat by poultry, fish, or legumes (61) and of potatoes by vegetables (58) and adherence to "healthful" dietary patterns (62) are also associated with a lower risk of GDM.

Physical exercise counselling

There are large differences in the proportion of women performing regular exercise before and during pregnancy. In Norway, the rate before pregnancy was 46.4 %, but declined to 28% and 20 % at 17 and 30 gestational weeks respectively (63). Studies in Denmark (64), the USA (65) or Brazil (66) showed a more pronounced reduction in physical activity even in uncomplicated pregnancies whereby activity positively correlated with the income. Most women do not meet recommendations for physical activity (66). Timing, intensity or kind of exercise (e.g. swimming, running or aerobics) within 4/17 SRs and meta-analyses was not specified and the compliance not controlled.

Combined counselling

Similarly, the overall and differential effects of combined diet *and* physical activity during pregnancy varied by the pattern, timing and the prevalence of exercise or nutrition.

Pharmacological counselling

Systematic reviews and meta-analyses to prevent GDM as a primary outcome. have involved metformin in obese women (67), myo-inositol (68) and probiotics (69). Metformin could decrease gestational weight gain but not GDM or perinatal mortality. Pregnant women should not use metformin to prevent GDM or poor pregnancy outcomes in obese non-diabetic women. In contrast, in women who are already diagnosed with GDM, metformin reduces HDP when compared with other treatments or placebo (70).

Four RCTs on antenatal supplementation with myo-inositol during pregnancy showed a potential benefit to reduce GDM. There were no differences for HDP, macrosomia or perinatal mortality when compared with controls. Only one RCT has shown a reduction in GDM when women used probiotics without data on HDP or fetal outcomes (69).

Conclusion

Strength of this narrative review is to increase awareness towards the increasing number and the quality of retrospective SRs and meta-analyses. Recently, Shennan indirectly criticized a lack of consistent primary evidence in so-called network meta-analyses which compare interventions of different quality studied at different places and times (71). Similarly, Prior published in this journal on “p-hacking” characterizing meta-analyses with a selection bias due to absent or delayed registration of the protocol or non-consistent outcome parameters (72). Nevertheless, this paper is insufficiently debated in the public. Another potential error is to apply Cochrane tools for RCTs which contain an item of blinding participants and personnel. This item is of limited value or even confusing for lifestyle interventions, since neither counselling health care specialists nor women following a diet or exercise program can be blinded (73).

Limitations of this review include that we could only summarize retrospective SRs, only 2/17 designed as an individual participant data meta-analysis (33, 47). Not all studies applied a sensitivity analysis. In addition, it has not yet been shown that fact boxes improve the understanding of parents-to be and the dialogue between them and their health care providers as demonstrated for other fields of medicine. Therefore, we are currently examining the acceptance in different social and patient groups.

We consciously concentrated on lifestyle interventions because a change in behavior during the sensitive period of pregnancy might convince women to play an active part in the health outcomes of themselves and their children. Pregnant women are particularly often in contact with the medical system and could be periodically informed about diet and exercise which are not associated with potentially undiscovered harms as compared to pharmacologic interventions.

In the future, *prospective* meta-analyses and Delphi procedures as already performed for GDM (74) may avoid weaknesses of retrospective SRs and improve the sources for counselling. Further studies should demonstrate whether increased awareness and compliance towards evidence-based counselling translates into better compliance or better outcomes of mothers and their offspring. In the meantime, editorial boards might critically analyze SRs and meta-analyses, so that only the best evidence is accepted and translated into patient counselling. Fact boxes and icon arrays could supplement the state-of-the-art of clinical research and guidelines for parents who must make decisions for or against screening tools, invasive procedures, medical treatments or the place of birth. This would allow women to be more independent of their health care providers’ views who may be biased by false incentives (75). Practices to increase the health literacy of pregnant women should become part of medical education. Finally, illustrations of essential information may help policy makers to decide whether the introduction of

interventions would fulfill the “Triple Aim” criteria to reduce costs and still increase individual satisfaction and the health of a society (76).

Abbreviations

BMI Body mass index,

CI Confidence interval

CVD Caridovascular disease,

DM Diabetes mellitus

EGWG Gestational weight gain,

FGR Fetal growth restriction

GDM Gestational diabetes mellitus

HDP Hypertensive diseases in pregnancy

IOM Insitute of Medicine

LGA Large for gestational age

OR Odds ratio

RCT Randomized controlled trail

RR Relative risks

SGA Small for gestational age

SR Systematic review

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Tables

Table 1) Summary of 4/17 systematic reviews and meta-analyses (35, 38, 44, 47) investigating lifestyle interventions to reduce gestational diabetes (GDM) and associated health outcomes. According to PRISMA only these 4 studies received 5 points allocated to each element (study question, literature search, data extraction, evaluation of results and registration) (48).

Authors / integrated studies/ Type of publication	Population (n) Characteristics	Specified intervention	Effect on GDM RR or OR (95%CI)	Fetal effects RR (95%CI)	Other significant effects RR/MD (95%CI)	Substantial heterogeneity I^2	Quality according to ROBIS criteria AMSTAR-1 & 2 tools
Tieu et al. 2017 n=11 Systematic review and meta-analysis	n=2786 All BMI categories, subgroups by BMI	Dietary advice, low GI, high fiber	Trend towards lower rate of GDM RR=0.60 (0.35-1.04)	No data available	Reduced gestational hypertension RR=0.30 (0.10-0.88) and weight gain MD=-4.70 kg (-8.07 -1.34)	I = 56%	Low risk of bias 11/11 & 15/16
Han et al. 2012 n=5 Systematic review and meta-analysis	n=1115 All BMI categories	Exercise not specified	No significant differences RR= 1.10 (0.7-1.84)	No significant differences	No data available	I<40	Low risk of bias 10/11 & 12/16
International weight management in pregnancy collabo-rative group 2017 n=36 Systematic review and meta-analysis	n=12526 All BMI categories	Diet & physical activity not specified	Trend towards lower rates of GDM OR= 0.89 (0.7- 1.1)	No data available	Reduced gestational weight gain MD-0.70 (−0.92−0.48) and Cesareans OR= 0.91 (0.83- 0.99)	I<40	Low risk of bias 9/11 & 12/16
Shepherd et al. 2017 n=23 Systematic review and meta-analysis	n=8918 All BMI categories	Diet, physical activity not specified	Trend towards lower rates of GDM RR=0.85 (0.71-1.01)	Trend towards lower rates of LGA : RR=0.91 (0.81-1.07), no differences in stillbirth: RR= 0.69 (0.35- 1.36)	Reduced gestational weight gain MD -0.89 (-1.39 -0.4)	I=42	Low risk of bias 11/11 & 15/16

BMI=body mass index, CI= confidence interval, GI=glycemic index, LGA= large for gestational age, MD=mean difference, OR=odds ratio, RR=risk ratio,

Figures

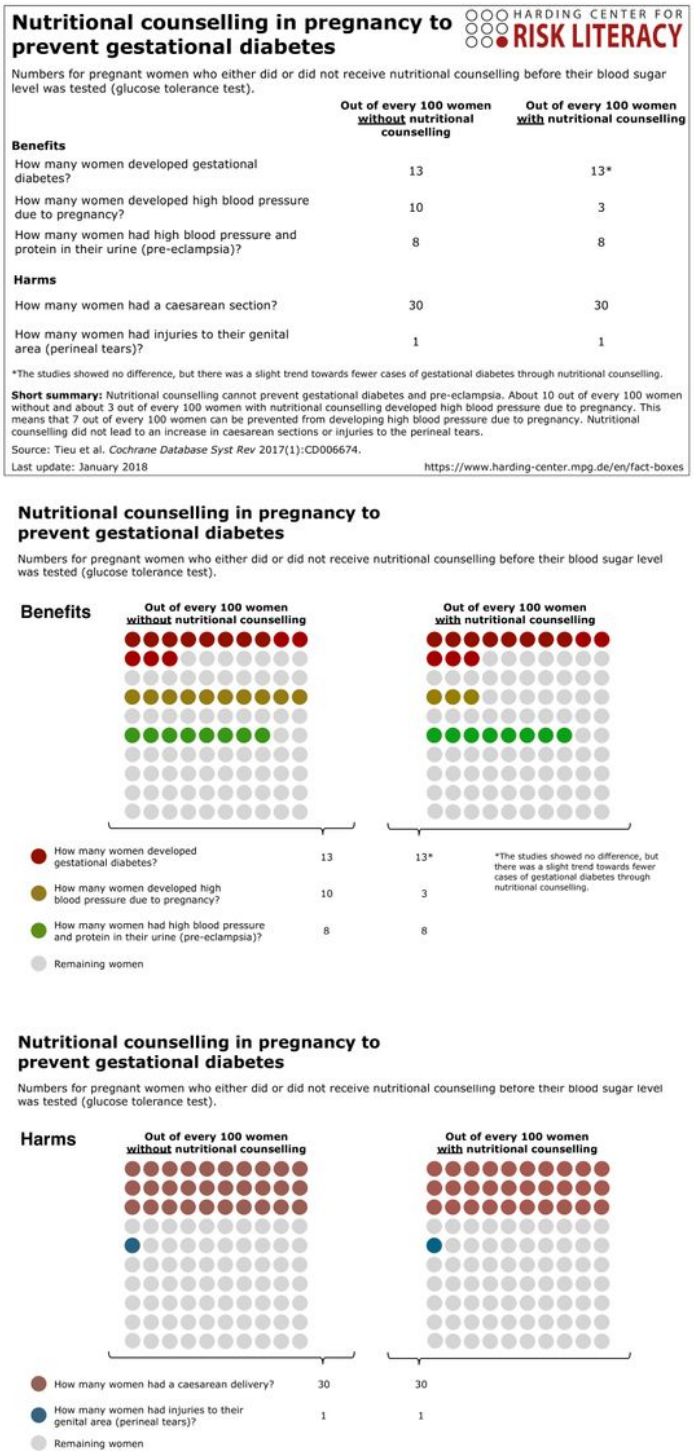

Figure 1

Fact box combined with an icon array designed to communicate the main patient-relevant benefits and harms of nutritional counselling for pregnant women to prevent gestational diabetes based on the Cochrane Review by Tieu et al. (35).