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Reproductive Health, 2014; 11(Suppl. 3):S5-1-S5-20

Originally published at:
http://doi.org/10.1186/1742-4755-11-S3-S5

Lassi et al. Reproductive Health 2014, 11(Suppl 3):S5
http://www.reproductive-health-journal.com/content/11/S3/S5

REPRODUCTIVE HEALTH

REVIEW Open Access

Preconception care: screening and management of chronic disease and promoting psychological health

Zohra S Lassi, Ayesha M Imam, Sohni V Dean, Zulfiqar A Bhutta*

Abstract

Introduction: A large proportion of women around the world suffer from chronic diseases including mental health diseases. In the United States alone, over 12% of women of reproductive age suffer from a chronic medical condition, especially diabetes and hypertension. Chronic diseases significantly increase the odds for poor maternal and newborn outcomes in pregnant women.

Methods: A systematic review and meta-analysis of the evidence was conducted to ascertain the possible impact of preconception care for preventing and managing chronic diseases and promoting psychological health on maternal, newborn and child health outcomes. A comprehensive strategy was used to search electronic reference libraries, and both observational and clinical controlled trials were included. Cross-referencing and a separate search strategy for each preconception risk and intervention ensured wider study capture.

Results: Maternal prepregnancy diabetic care is a significant intervention that reduces the occurrence of congenital malformations by 70% (95% Confidence Interval (CI): 59-78%) and perinatal mortality by 69% (95% CI: 47-81%). Furthermore, preconception management of epilepsy and phenylketonuria are essential and can optimize maternal, fetal and neonatal outcomes if given before conception. Ideally changes in antiepileptic drug therapy should be made at least 6 months before planned conception. Interventions specifically targeting women of reproductive age suffering from a psychiatric condition show that group-counseling and interventions leading to empowerment of women have reported non-significant reduction in depression (economic skill building: Mean Difference (MD) -7.53; 95% CI: -17.24, 2.18; counseling: MD-2.92; 95% CI: -13.17, 7.33).

Conclusion: While prevention and management of the chronic diseases like diabetes and hypertension, through counseling, and other dietary and pharmacological intervention, is important, delivering solutions to prevent and respond to women's psychological health problems are urgently needed to combat this leading cause of morbidity.

Introduction

Preconception care for women with underlying chronic diseases is very crucial. Worldwide, 60 million women of reproductive age have type-2 diabetes [1]. While diabetes has known macro- and micro-vascular complications, this increasing prevalence in women of reproductive age makes it a serious health concern for those to-be mothers and their newborns. Diabetes during pregnancy is associated with increased risk for miscarriages, stillbirth, macrosomia and obstetric complications, intrauterine developmental and growth abnormalities, birth and neonatal complications [2,3]. Strict control of blood glucose during pregnancy is necessary, however counseling, diet modification and tight glycemic control in the preconception period offer a greater benefit to maternal and newborn outcomes.

Thyroid disease is another prominent chronic illness in women of child-bearing age, second only to diabetes. Thyroid hormone imbalances during pregnancy, particularly during the first trimester, are known to cause intellectual impairment of the offspring as well as pregnancy complications including hypertension and preeclampsia, placental

* Correspondence: zulfiqar.bhutta@aku.edu
Division of Women and Child Health, Aga Khan University Karachi, Pakistan

abruption, anemia, postpartum hemorrhage, preterm birth, low birth-weight and fetal death [4].

Phenylketonuriais an important metabolic disorder that has been associated with neurological sequelae and congenital heart defects in neonates if levels of phenylalanine are not controlled during pregnancy [5]. Therefore, the most favorable period to achieve control is before conception.

Other than the physical health of women of child bearing age, their mental health is equally important in ensuring healthy outcomes for both mother and child. Mood and anxiety disorders are highly prevalent among women of reproductive age and there is evidence that new-onset illness or a relapse is highly prevalent during pregnancy [6]. Psychiatric disorders during pregnancy have been associated with poor obstetric outcomes, higher risk of postpartum psychiatric illness, increased rates of substance abuse, and lower participation in prenatal care leading to adverse infant outcomes [7,8]. Intimate partner violence (IPV) has serious consequences for women's psychological and physical health. Victims of IPV are at high risk of unplanned pregnancy due to sexual coercion.

Prior to taking on the challenge of supporting another life, women should be in their optimal physical and psychological health. This paper highlights the maternal and fetal risks from uncontrolled chronic diseases and potential interventions that have been effective in alleviating these risks. This paper has also assessed the risks associated with psychological health and IPV in particular and the interventions that have met with some success in dealing with these.

Methods

This paper systematically reviewed all the literature published up to 2011 to identify studies describing the effectiveness of preconception interventions (any intervention provided to women and couples of childbearing age, regardless of pregnancy status or desire, before pregnancy or between two pregnancies, to improve health outcomes for women, newborns and children period before pregnancy and between pregnancies) and risks for preventing and managing chronic diseases and promoting psychological health for improved maternal, newborn and child health (MNCH) outcomes. Electronic databases such as PubMed, Cochrane Libraries, Embase, and WHO Regional Databases were searched to identify the experimental and observational studies on the subject. Papers were also identified by hand searching references from included studies. No language or date restrictions were applied in the search. The findings were presented at international meeting [9,10] and shared with professionals in the relevant fields of maternal and child health, following which results were updated based on current searches (through end of 2012) and expert opinion. Studies were included if they reported the effectiveness of interventions for preventing and managing chronic diseases and promoting psychological health on MNCH outcomes. The methodology is described in detailed elsewhere [11].

Two authors assessed the eligibility of studies and extracted data and judged the quality on standardized sheets. The quality of experimental studies were assessed using Cochrane criteria [12], whereas STROBE guidelines were used to assess the quality of observational studies [13]. We conducted meta-analyses for individual studies and pooled statistics was reported as the odds ratio (OR) and relative risk (RR) between the experimental and control groups with 95% confidence intervals (CI). Mantel–Haenszel pooled RR and corresponding 95% CI were reported or the Der Simonian–Laird pooled RR and corresponding 95% CI where there was an unexplained heterogeneity. All analyses were conducted using the software Review Manager 5.1 [14]. Heterogeneity was quantified by Chi^2 and I^2, in situations of high heterogeneity, causes were explored through sub-group analysis and random effect models were used.

Results

The review identified 2065 papers from search in all databases. After the initial title and abstract screening, 187 full texts were reviewed to identify papers which met the inclusion criteria and had the outcomes of our interest. One hundred and sixty one studies were finally selected for abstraction and analysis (Figure 1). Information related to each included study can be found on the following link:

https://globalmotherchildresearch.tghn.org/site_media/media/articles/Preconception_Report.pdf

Diabetes

Diabetes continues to be an ever-increasing global problem. The prevalence of Type 2 (characterized by hyperglycemia in the context of insulin resistance and relative lack of insulin) diabetes continues to increase worldwide [15,16], especially in the low and middle income countries (LMICs) [17,18]. This in turn means more women of reproductive age in LMICs have diabetes, hence a greater number of pregnancies are complicated by the condition [19,20] putting both the mother and the fetus at an increased risk of morbidity and mortality [21]. Diabetes in pregnancy is associated with elevated rates of miscarriage [22], pre-eclampsia [23,24], preterm labor and caesarean sections [25,26] and higher rates of fetal malformation [2,3,25,27] neural tube defect, urinary tract disorder, macrosomia [28,29], birth injury [26,27,30], and perinatal mortality [31,32].

Preconception diabetic care is a multidisciplinary approach with the goal of care being to obtain the lowest

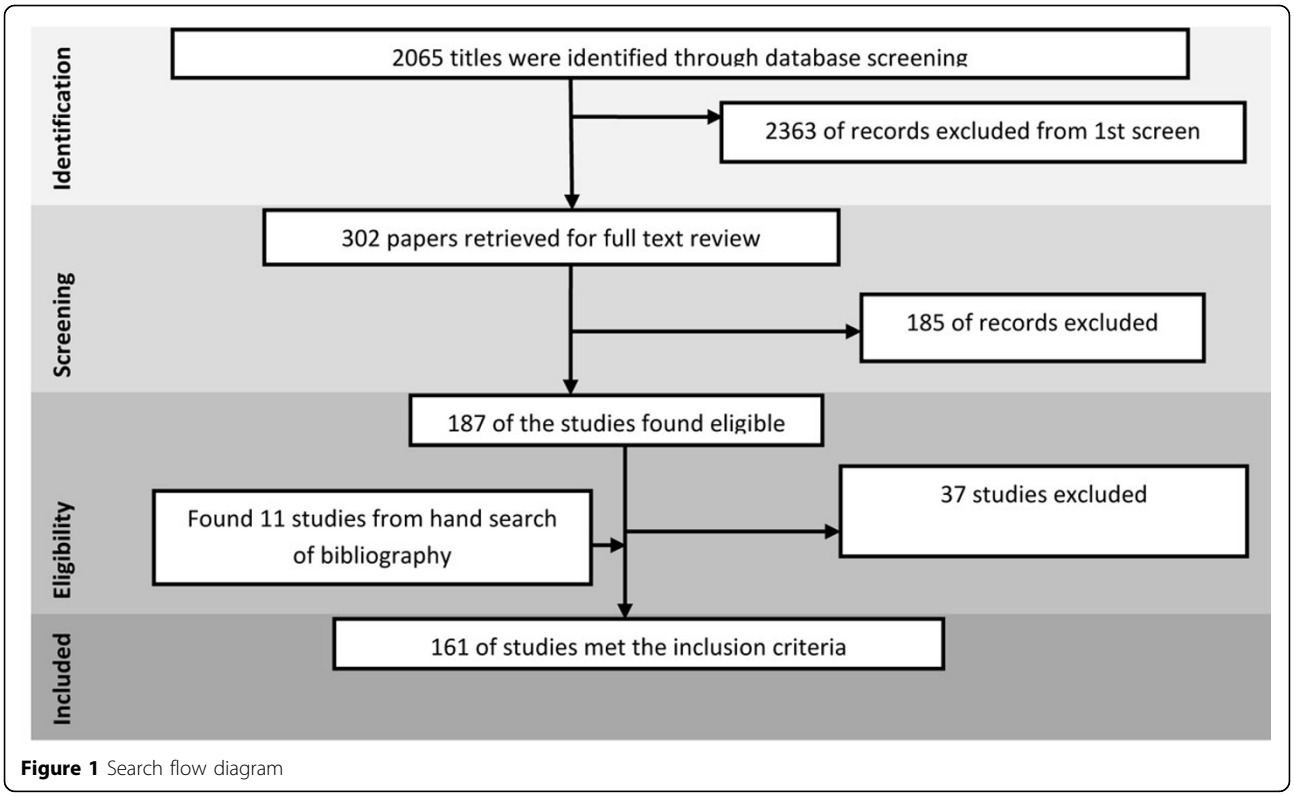

Figure 1 Search flow diagram

possible hemoglobin A1C without significant episodes of hypoglycemia. The content for preconception care broadly includes educating the patient with regards to the disease and its interplay with pregnancy; educating the patient about self-management skills; physician-directed assessment and care of the disease and complications; counseling about diet, exercise and reproductive advice.

The review identified 22 observational studies [32-53] and one trial [54] that looked at various outcomes related to pre-gestational diabetes. Meta-analysis of 21 studies showed that preconception care was able to reduce the occurrence of congenital malformations (RR 0.30; 95% CI: 0.22-0.41) (Figure 2). Pooled data for the effect of preconception care on the risk of perinatal mortality was also significant (RR 0.31; 95% CI: 0.19-0.53) with counseling plus strict glycemic control leading to a 71% reduction in the events in this group compared to the standard antenatal care group (Figure 3).

When looking at pregnancy complications, the meta-analysis supported the effectiveness of preconception care in non-significantly reducing the rate of preterm delivery (RR 0.83; 95% CI: 0.62-1.12) and of caesarean sections (RR 0.97; 95% CI: 0.77-1.23) [39,41,48,50,53]. Results for other fetal/neonatal outcomes [53] and macrosomia [48,50,51] were also non-significant. The data revealed that preconception care was valuable in significantly dropping the level of HbA1C during the first trimester of pregnancy (MD -1.71; 95% CI: -2.72,-0.71) [32-34,38,40,45-47,55,56]. As hyperglycemia during the period of organogenesis leads to an increased risk of congenital malformations, this achievement of better glycemic control in the 1st trimester may explain the concurrent reduction of anomalies as well as subsequent perinatal death. A single study by Heller et al. [54] showed a weak non-significant effect of preconception insulin in reducing the 1st trimester HbA1C as compared to commencement of insulin in early pregnancy (MD -0.10; 95% CI: -0.27, 0.06).

Epilepsy management

Epilepsy is a condition in which a disruption of the normal electrochemical activity of the brain results in seizures. Women with epilepsy during their child-bearing years not only face the possible risk for adverse pregnancy outcome as a result of the teratogenic effects of antiepileptic drugs upon [57,58] but also the potential effect of maternal seizures on the developing fetus [59-61]. Most women with epilepsy have no change in seizure frequency during pregnancy but about 15-33% report increased episodes of seizures during pregnancy [62]. This may be due to a change in the pharmacokinetics of the anti-epileptic drugs [63] or due to the hormonal changes occurring in pregnancy [64]. Unplanned pregnancies rates in women are high but these may be

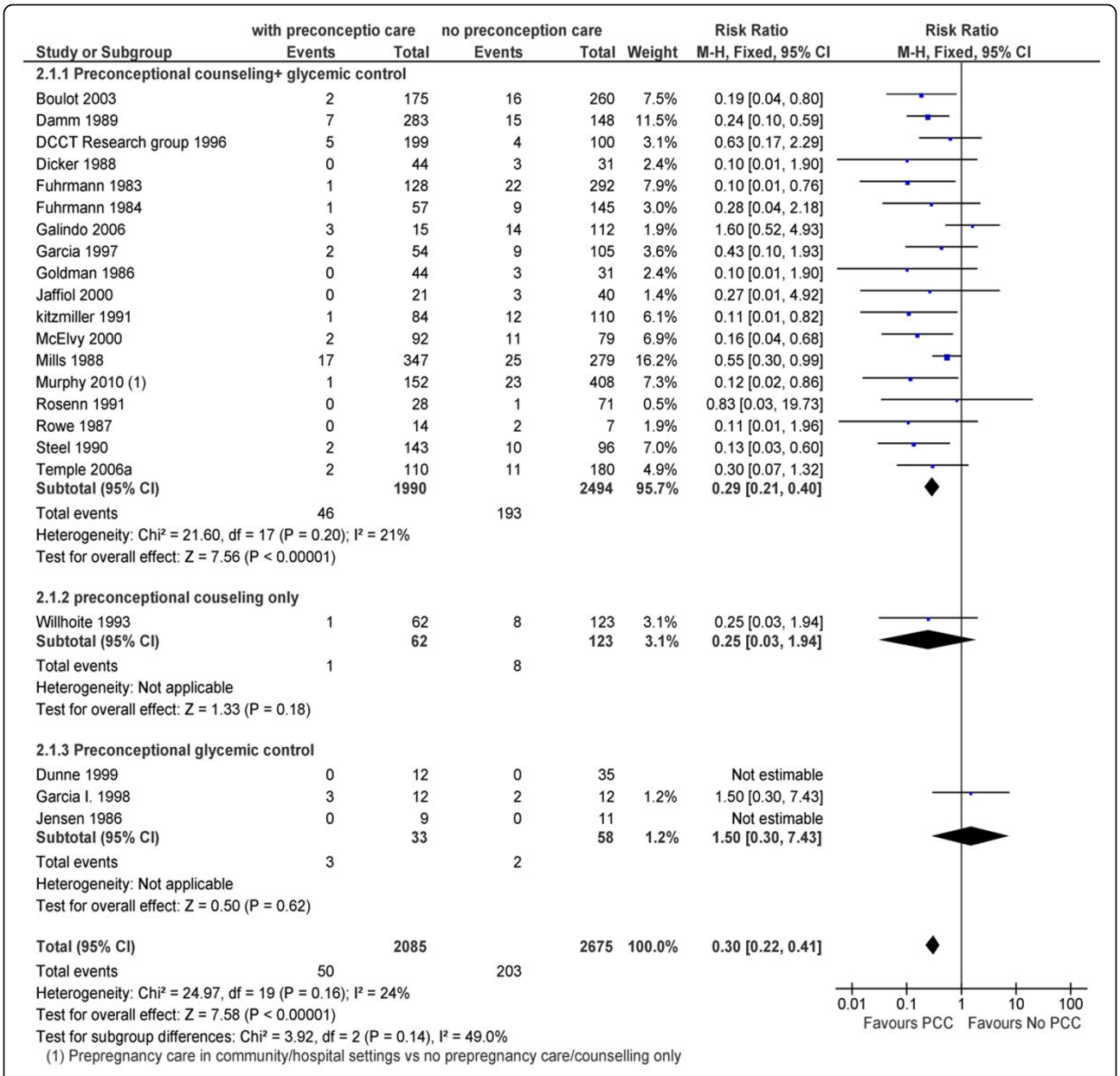

Figure 2 congenital malformations in preconception care versus non preconception care: evidence from observational study

even higher in women with epilepsy because antiepileptic drugs interfere with hormonal contraception [65]. Different drugs lead to different types and different rates of anomalies, with the highest rates being associated with valproate [66,67].

Preconception care of women with epilepsy includes a careful revision of each case to ascertain the diagnosis, the need for continued anti-epileptic drug therapy, selection of suitable drugs with optimization of the dosage, and prescription of folic acid to prevent neural tube defects.

We found one study [68] that assessed the effectiveness of preconception counseling in women with epilepsy reported that none of the 85 women who were counseled before pregnancy had an abnormal fetus in the subsequent pregnancy as compared to almost 19% of the women who did not receive any preconception counseling (as they were already pregnant) who had an abnormal fetus (with 3 pregnancy terminations). One patient in the counseled group had an early miscarriage, followed by a normal subsequent pregnancy, and 1 had a preterm birth compared to 3 preterm births in the control group. They also showed that post-counseling 71% of women with epilepsy used a single drug and none used >2 drugs as compared to 32% and 20% respectively in the control

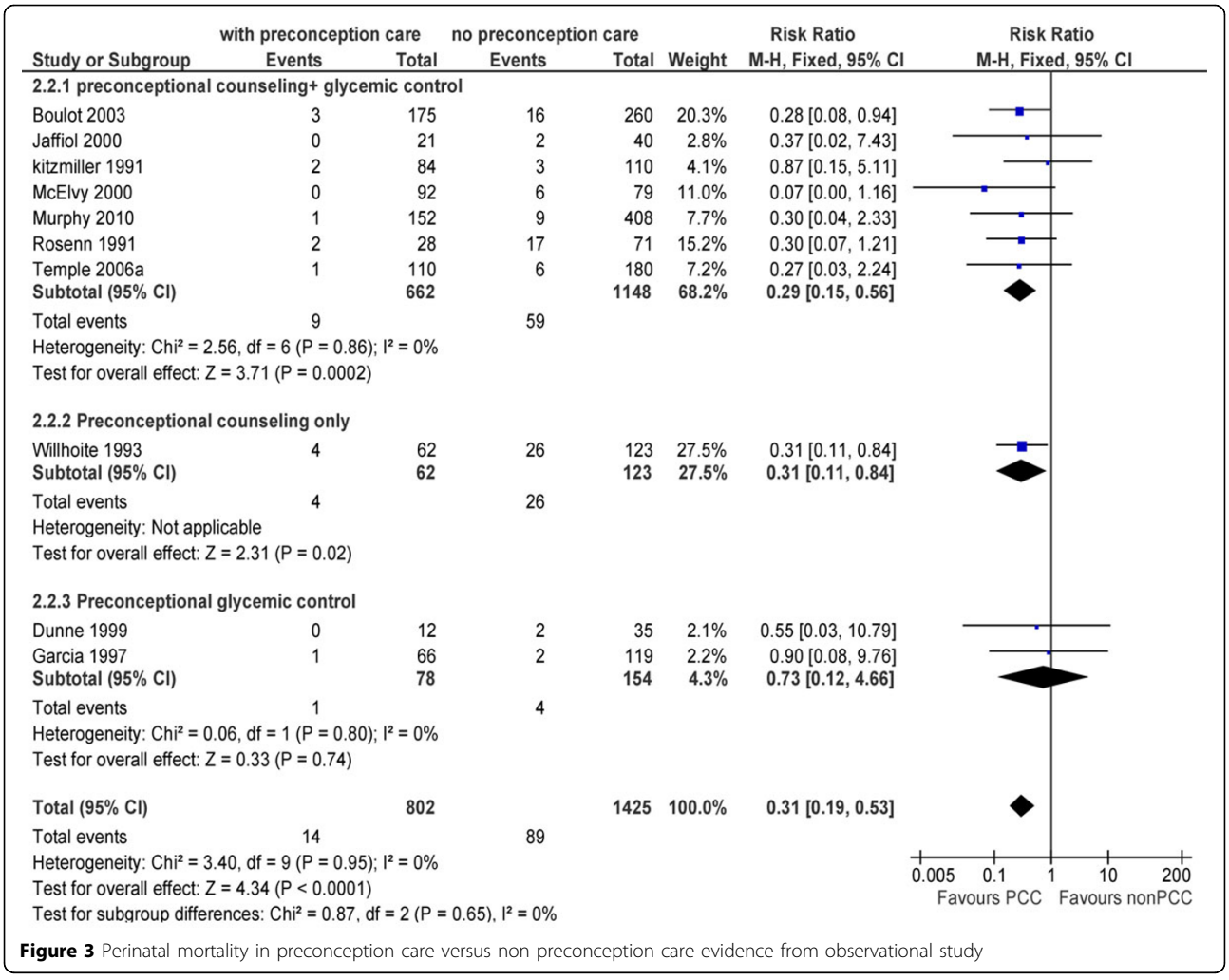

Figure 3 Perinatal mortality in preconception care versus non preconception care evidence from observational study

group. Most of the counseled women used carbamezapine/lamotrigine compared to the control women with epilepsy, 41% of whom used valproate.

Management of phenylketonuria

Phenylketonuria (PKU) is caused by the deficiency of phenylalanine hydroxylase which is required to essential amino acids, phenylalanine (phe), to tyrosine [69]. These women are advised to consume phe free food to live a normal life. These women during pregnancy require appropriate management as poor disease control is associated with a multitude of fetal consequences like facial dysmorphism, microcephaly, developmental delay, learning difficulties and congenital heart disease [69,70].

This review accumulated evidence from current literature on the effect of maternal PKU on the pregnancy outcome, specifically of preconception levels of phenylalanine. The review also looked for any preconception intervention which worked in lowering the maternal, newborn and child health (MNCH) risks associated with poorly controlled phenyalanine levels. Preconception care of women with PKU consists of counseling regarding the fetal risks (facial malformations, growth deficits, micorcephaly) associated with the disease, commencement of a phenylalanine restricted diet, attaining safe phenylalanine levels (100 [71] −360μmol/L [72] or <6mg/dL [73,74] atleast 3 months before conception; and maintaining them throughout gestation). When counseling patients great importance has to be put on the need for effective contraception till such safe levels are reached.

The review identified seven studies [70,75-80]. Rouse et al. [70] in a cohort of women with blood Phenylalanine levels >240umol/L found that mean phenylalanine levels at 4 to 8 weeks gestation predicted congenital heart defect (P<0.0001). They also found that each abnormality increased in frequency as Phenylalanine control was delayed. The percentage of offspring with >3 dysmorphic features (49% overall) was related to time of inadequate maternal Phenylalanine control

(P=0.002), increasing from 19% in offspring of mothers in control before pregnancy to 62% when control was not achieved before 20 weeks' gestational age. The frequency of offspring with microcephaly was significantly related to time of maternal Phenlalanine control (P=0.001)- in women who were preconceptionally treated with good control, microcephaly occurred in only 3.6% of the pregnancies [5].

From current literature the effect of a preconception dietary intervention was analyzed for growth of the fetus. The analysis showed that a strict preconception diet was significantly associated with an increment in mean birth weight (MD 0.60; 95% CI: 0.39-0.82) and increase in head circumference (MD 3.20; 95% CI: 2.37-4.03) compared to no dietary restrictions [80]. Improved infant growth markers were also associated with following a strict preconception diet in other studies [75,79]. Koch et al. [75] reported that a preconception diet led to a 1st trimester PHe level of 500umol/L compared to 641umol/L in those on a post conception diet. Maillott et al. [76] also reported a significant decrease in 1st trimester mean PHe level in those on a preconception diet versus a post-conception diet [248.8+/-86.6 compared with 493+/-289.4mol/L; P<0.0001].

Addressing thyroid disorders preconceptionaly

Women of child bearing age may suffer from hypo- or hyper-function of the thyroid gland, more often than not due to an autoimmune process. Hypothyroidism during pregnancy is known to lead to adverse maternal (gestational hypertension and pre-eclampsia [81], postpartum hemorrhage, abortion [4] and preterm delivery [82,83]), fetal (congenital anomalies, growth retardation [84], perinatal death) [82] and neonatal consequences (cognitive disorders) [85]. Literature on the association between thyroid disease during pregnancy and preterm delivery is most abundant, with most attributed to autoimmune thyroid disease [86-89]. Among the most frequent complications are the hypertensive disorders of pregnancy, also reported are spontaneous abortion and preterm delivery [90].

While literature on the effect of thyroid status on maternal, fetal and neonatal effects is abundant, much work still needs to be done with regards to the effect of preconceptional thyroid status on these outcomes. Many recommend attainment of a TSH <2.5mU/L before the start of pregnancy. Since purely preconception literature was unavailable, the review looked at the effect of periconceptional interventions addressing adverse pregnancy related outcomes and even those studying the effect of the disease and treatment on MNCH outcomes. Content of preconception care for women with thyroid disorders consists of a thorough assessment of the disease status, advice on the achievement of a euthyroid status well before conception, counseling about the pregnancy-related risks associated with thyroid dysfunction. Medications need to be adjusted in order to have optimal thyroid function and the importance of useful contraception should be stressed upon till such a time.

Thyroid status at the time of conception plays an important role. According to the study by Abalovich et al. [85] none of the women who were euthyroid at the time of conception experienced preterm deliveries. Mestman et al. [91,92] underscores the importance of pre-pregnancy counseling for hyperthyroid women and the use of contraception until achievement of a euthyroid status before conceiving. Earl et al. [93] found no interventions for the prevention and treatment of hyperthyroidism during pregnancy. Their result for usage of antithyroid drugs (ATD) was inconclusive due to the small potential risk of adverse fetal effects of methimazole and maternal effects of propylthiouracil. Another study reports that both ATDs are equally effective and safe in the treatment of hyperthyroidism in pregnancy [94]. Periconception use of ATD was however; shown to significantly increase the rates of selected birth defects (Figure 4) [95].

Browne et al. [95] also reported an association of periconception thyroxine and selected birth defects. Rotondi et al. [96] conducted a trial on the preconception adjustment of levothyroxine and found that it may lead to adequate thyroid function in the 1st trimester; however they did not look at any MNCH outcome. Results suggest that in hypothyroid women anticipating pregnancy (with serum TSH in the lower quartile of normal range), the pre-conception adjustment of L-T4 doses may result in adequate maternal thyroid function up to the first post-conception evaluation [96].

Vaquero et al. [97] reported that in thyroid supplementation group (66mg of thyroid extract, started before conception and continued until the 20th week) among patients with thyroid antibodies, 13 out of 16 pregnancies (81.2%) ended in live birth. Only one pregnancy loss occurred among patients with a mild underlying thyroid pathology treated with thyroid replacement therapy.

Systemic lupus erythromatoses and other connective tissue diseases

Systemic lupus erythematous (SLE) predominantly affects women in the childbearing age group, and thus the effect of pregnancy on the disease and vice versa is an important consideration in the management of these patients. Despite all the advances in understanding the disease pathology and management options pregnancy in lupus is still considered to be a high-risk pregnancy [98]. There is a higher rate of fetal loss, pre-term delivery and IUGR in lupus pregnancies [98-100]. Pre-existing hypertension or renal dysfunction further increases the risk of pre-eclampsia and pregnancy-induced hypertension (PIH) [100-102]. Several studies have found the frequency of

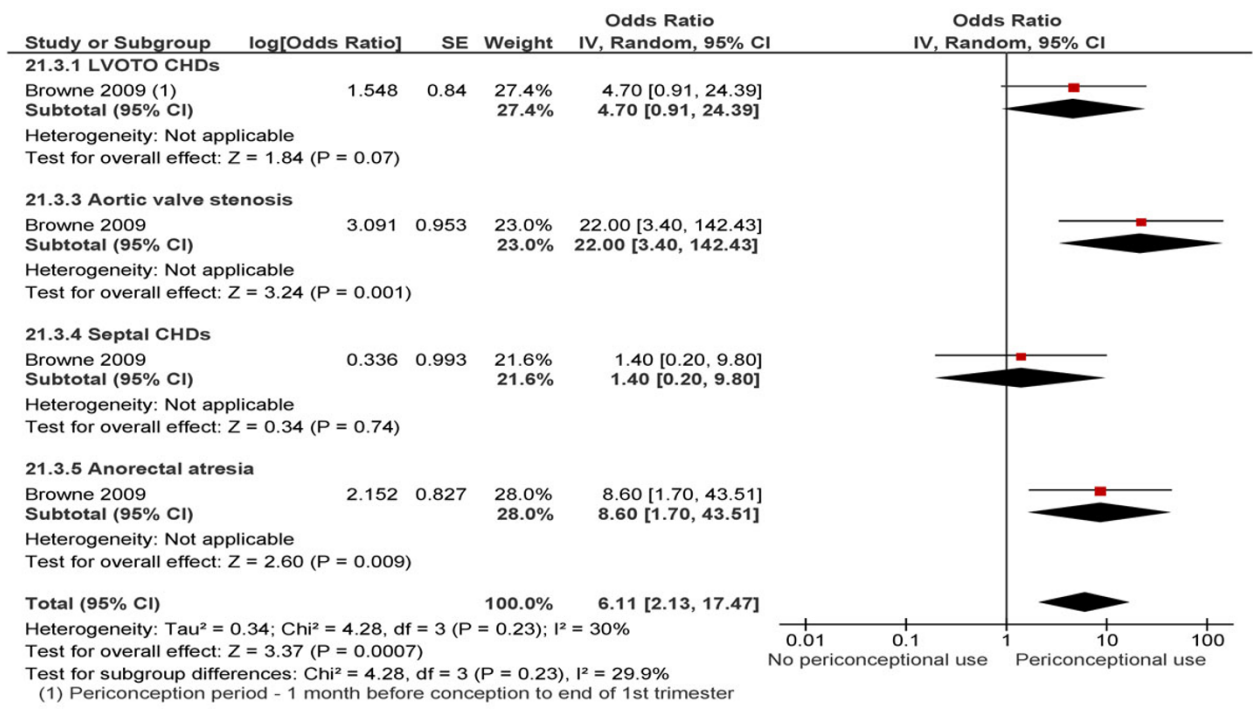

Figure 4 Periconception use of anti-thyroid medications and Birth defects evidence from observational study

fetal loss to vary between 11-24% [99,103-106]. While some studies advocate that active disease increases the risk of fetal loss [104,107,108], other studies show no statistically significant difference between pregnancies in women with active lupus and those in women with inactive lupus [109,110]. Active disease at conception is a known predictor of poor outcome [102,109,111]. A flare during the year prior to conception pointed to increased risks of a flare again during pregnancy [112,113].

SLE is a prime example of an autoimmune disorder. The review used this disease to study the possible effects of autoimmunity on MNCH outcomes. The review also looked at the effects of treatment modalities for SLE and how, if any available intervention (like counseling, behavioral programs) targeting such women improved the pregnancy outcomes.

The review found a number of observational studies looking at the effect of active disease in the preconception period on pregnancy related outcomes [77,102,108,109, 114-128]. The analysis showed that preconception active SLE was associated with multiple maternal and fetal/neonatal outcomes. An active disease increased the risks of gestational flares by 77% (P 0.04) (Figure 5) [117,123, 125-127]. There was an over three-fold increase in the risk of developing PIH if the disease was active (specifically with nephritis) before pregnancy (p=0.002); no association was found with risk of preeclampsia. There was also a significant rise in the preterm deliveries if the disease was not in remission before conception (RR 1.71; 95% CI: 1.18-2.48); this risk was further increased by 13% if the woman suffered from active nephritis pre-pregnancy.

Coming to adverse SLE related fetal/neonatal outcomes, it was seen that a positive disease activity in the preconception period significantly increased perinatal mortality (RR 2.42; 95% CI: 1.06, 5.51) (Figure 6) [102,108,117,123,125,127,128]. No association was seen with either spontaneous abortions (RR 3.26; 95% CI: 0.58-18.14) [108,123] or restricted fetal growth (RR 0.61; 95% CI: 0.16-2.28) [127]. Similar findings were reported by Smyth et al. [129].

Other chronic conditions

Chronic hypertension and heart disease – pregnancies complicated by chronic hypertension are associated with increased risk of hypertensive disorders of pregnancy and other organ dysfunctions as well as increased fetal risks of preterm birth, intrauterine growth retardation, fetal loss, hypospadias and abruption placenta [130].

Romunstad et al. [131,132] found a significant association between prepregnancy systolic as well as diastolic blood pressure and low birth weight (LBW). Magnussen et al. [133] found systolic blood pressures of greater than 130mmHg to increase the risk of pre-eclampsia by more than 7 times. Because there is an increasing burden of unplanned pregnancies, fetal exposure to antihypertensive medications might occur before a woman knows she is

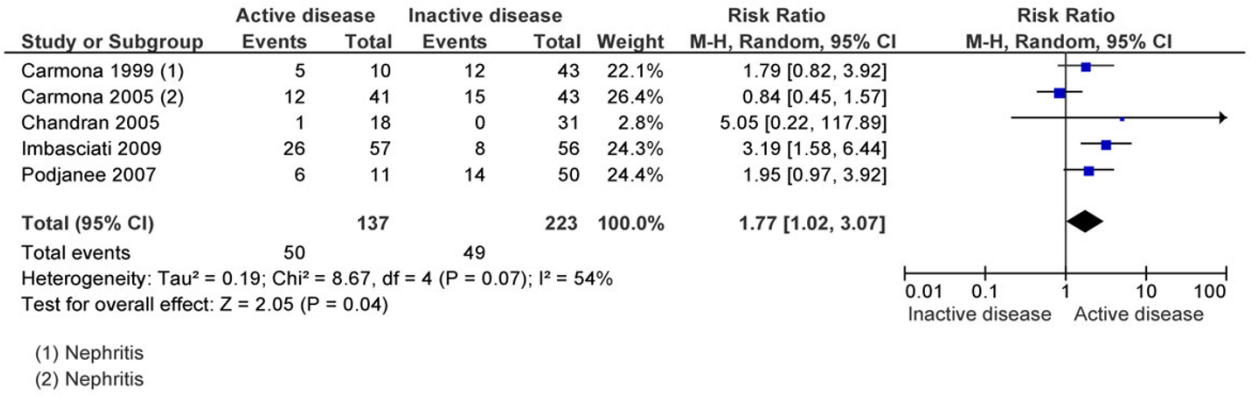

Figure 5 Preconception disease activity and disease flares during pregnancy evidence from observational study

pregnant. Caton et al. [130] studied the effect of periconception use of anti-hypertensives and found a positive association with the occurrence of hypospadias (OR 1.90; 95% CI: 1.00-3.61) [130], with a non-significant increase with exposures only to antiadrenergic agents at any time between 1 month preconception and the fourth month of pregnancy. Hameed et al. [134] found an increased risk of spontaneous abortion, cardiac anomaly (4-14%) in the presence of maternal congenital heart disease (CHD).

Asthma - Research demonstrates that women with severe asthma prior to pregnancy is more likely to worsen during pregnancy. This reinforces the importance of adequate asthma control prior to conception [135]. Asthma that is not adequately controlled during pregnancy can result in serious maternal complications (preeclampsia, hypertension, and hyperemesis gravidarum) [136] as well as increased fetal complications (stillbirth and infant death, neonatal hypoxia, intrauterine growth retardation, premature birth, and LBW) [137]. It is observed that the dangers of uncontrolled asthma are greater than the risks of indispensable asthma medications. Whereas oral corticosteroid use in the first trimester has been associated with reduced birth weight, an increased risk of preeclampsia, and an increased risk of oral clefts [138,139]. Analysis showed that periconception use of asthma medications was significantly linked to a greater risk of gastroschisis (OR 2.12; 95% CI: 1.39-3.24) [140] especially the use of bronchodilators which significantly doubles the risk.

Chronic renal disease- Adverse pregnancy outcomes associated with maternal renal disease include preeclampsia, anaemia, chronic hypertension, caesarean delivery, preterm delivery, fetal growth restriction, and increased fetal loss and stillbirth [141,142]. Renal hypertension is associated with a 10-fold increase in fetal loss compared to women with spontaneously or therapeutically normal blood pressures [143].

Headache – frequent pre-pregnancy headaches were found to be statistically significantly associated with poor mental health in the first 3 months of gestation as well as with antepartum depression [144].

Multiple sclerosis - Vukusic et al. 2004 [145] reported that women with greater disease activity in the year before pregnancy have a higher risk of relapse in the postpartum 3 months (OR 1.3, p 0.04).

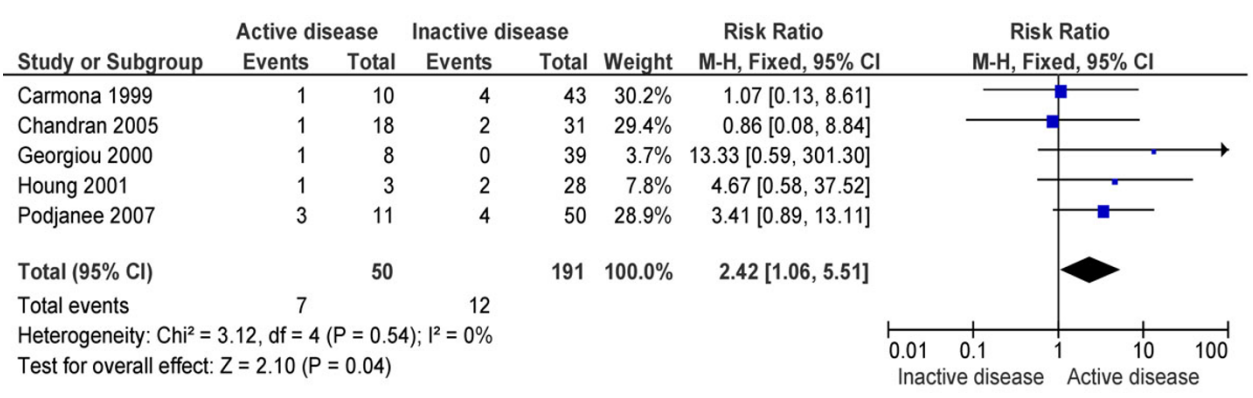

Figure 6 Preconception disease activity and perinatal mortality evidence from observational study

Medication use

Medication usage among pregnant women and women of reproductive age is common. It has been estimated that more than 80% of pregnant women take over-the-counter or prescription drugs during pregnancy [146]. National surveys among women of reproductive age document that chronic conditions often requires the ongoing administration of medications for maintenance are not uncommon among women of reproductive age [147]. As maternal age and body mass index increases, it is likely that an even greater proportion of women who are planning a pregnancy or who could become pregnant will have chronic diseases that necessitate prescription medications. Generally, medication carries a risk of unwanted side-effects which may have profound impacts during pregnancy.

The aim was to look for studies assessing interventions dealing with the repercussions of various medications being frequently used by women. Regular medications being used by women suffering from chronic diseases are covered in the sections of their respective disorders. Studies particularly addressing the deleterious effects of medications, on the health of both the mother and the fetus, when taken in the period before conception were assessed. The review found studies assessing the effect of use of weight-loss drugs, oral contraceptives and vasoactive agents.

Weight loss drugs - Analysis of the effect of periconception use of weight-loss drugs showed a significant association with overall higher rates of congenital anomalies (OR 1.59; 95% CI: 1.33-1.89) [148]. This association was stronger for congenital heart defects with an 88% increase in incidence of Dextro-Transposition of the great arteries and a 58% increase in the incidence of Left Ventricular Outflow Tract Obstruction (LVOTO) (OR 1.88; 95% CI: 1.33-2.65); (OR 1.58; 95% CI: 1.22-2.04) respectively. Bitsko et al. [148] reported the association with 'Aortic Stenosis' to be highest among the LVOTO defects (OR 1.2; 95% CI: 0.5-3.1).

Oral contraceptive pills (OCPs) – several studies identified that reported OCPs and maternal and fetal outcomes [133,149-151] No significant association was found between pre/peri-conception use of oral contraceptives and gestational hypertension [150], pre-eclampsia [133,150], preterm delivery, spontaneous abortion (Figure 7), however periconception use of oral contraceptive pills (OCP) lead to an almost three-fold increase in the risk of Down's in infants (RR 2.71; 95% CI: 1.48-4.95) [151].

Vasoactive substances - Werler et al. [152] reported aspirin use in the periconception period led to a significantly greater risk of amniotic bands (OR 2.5; 95% CI: 1.4-4.6). Vasoconstrictor and decongestant use led to a higher incidence of transverse limb defects (OR 1.4; 95% CI: 1.1-2.0) and (OR 1.7; 95% CI: 1.2-2.3) respectively.

Anti-hypertensive medications - Caton et al. 2008 [130] observed slight to moderate elevations in the risk of severe hypospadias for maternal untreated hypertension (OR 2.1; 95% CI: 1.6-2.9) and antihypertensive medication use during 1 month preconception through pregnancy month 4 (OR 1.4; 95% CI: 0.7-2.9).

Bronchodilators – Lin et al. 2008 [140] reported significant association of maternal bronchodilator use with gastroschisis (OR 2.06, 95% CI: 1.19, 3.59).

Thyroxin – Few studies [95,96,153] reported non-significant association with birth defects (OR 1.7; 95% CI: 1.0-2.7).

Any illness/common cold - A study by Krapels et al. 2006 [154] displayed an association of any maternal illness and common cold in periconception period (3 months before conception to 3 months after) with orofacial defects. Cleft lip with or without cleft palate increases by 1.7 times (95% CI: 1.2-2.5) and cleft palate only by 1.5 times (95% CI: 0.8-2.6).

Mental health

With the current prevalence of psychiatric illnesses, there is a significant risk of women's antenatal and postpartum periods being made difficult with the onset or recurrence of a psychiatric illness. Evidence suggests that depression and anxiety during pregnancy and postpartum severely impact family life, the mother-infant relationship, and the future mental health of the child [6-8,155]. A large meta-analysis stated that up to 18% of women experience depressed mood during pregnancy [156]. A Brazilian study noted that common mental disorders, in general, were autonomously related with LBW and post-traumatic disorder (PTD) in pregnant teenagers javascript:newshowcontent('active','references'); [157]. Maternal antenatal depression generally has been highly correlated with PTD [158-160]. Similarly, depression also appears to be a significant risk factor for LBW [159,161,162]. Depression also has noteworthy associations with miscarriage, antepartum hemorrhage, greater uterine artery resistance and a higher risk of operative deliveries [161]. Additional risks are associated with the medications being used to treat depression. Selective serotonin reuptake inhibitor (SSRIs) has been linked with earlier gestational age and lower birth rate [163,164]. Other studies also suggest first trimester exposure to SSRIs increasing the risks restricted fetal growth [165,166].

Bipolar disorder is a severe recurrent illness that is associated with high rates of morbidity and mortality in the absence of adequate treatment. Manic episodes may be associated with increased risky behaviors such as sexual activity or substance use, which could affect health during pregnancy as well as lead to a significant risk of unintended pregnancies [167]. Patients with bipolar disorder

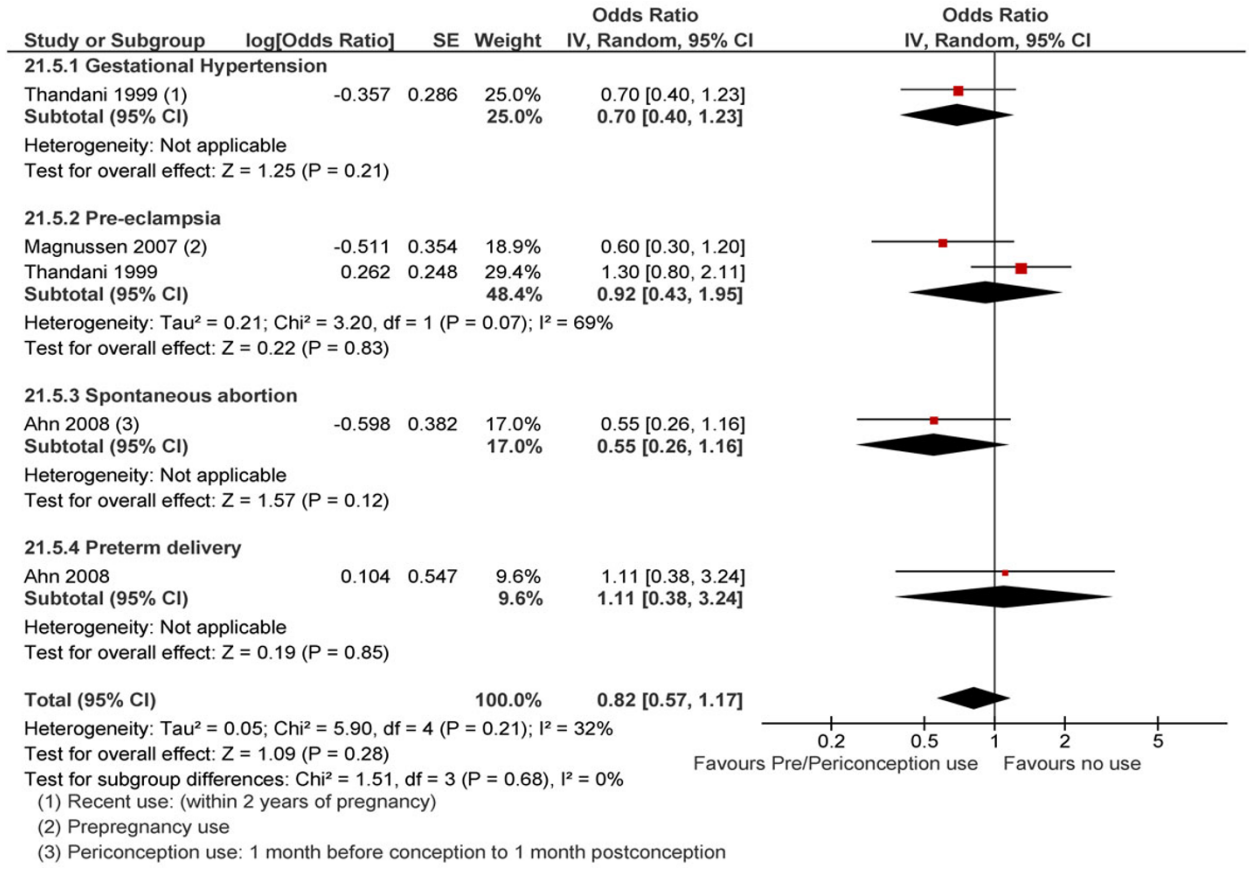

Figure 7 Pregnancy outcomes of Pre/Periconception use of oral contraceptives evidence from observational study

have a very high risk of comorbid alcohol or substance abuse disorders – reaching up to 60% in some studies - which could have direct adverse impacts on fetal outcomes [168,169].

The review assessed the effect pre-existent psychiatric conditions in women in the preconception period on maternal and fetal morbidity and mortality. Included were more prevalent conditions like mood disorders as well as conditions like schizophrenia. The review looked primarily at the risks and benefits, to the mother as well as her unborn child, of continuing or changing or even discontinuing the psychotropic regimens for the above mentioned disorders.

While the effect of psychiatric conditions and their relative treatment during pregnancy has been widely studied [170-189], there is a serious lack of evidence of how pre-pregnancy disease and psychotropic drugs may affect pregnancy. The review found that pre-pregnancy depression is significantly related to preterm births (OR 1.04; 95% CI: 1.02-1.07) [171] and adolescent depression per say was significantly associated with an increased risk of miscarriages (OR 2.25; 95% CI: 1.12-4.50) [172]. When assessing for maternal morbidity, adolescent depression was positively associated with suffering from intimate partner violence (IPV) (OR 3.47; 95% CI: 1.11-10.84) but not with sexually transmitted infections (STIs) (OR 1.50; 95% CI: 0.83-2.72) [172]. Silverman et al. [173] concluded that a pre-existing psychiatric condition was one of the best predictors of development of post-partum depression. Literature also showed that a pre-pregnancy psychotic or bipolar illness substantially increased the risk of a postpartum psychotic or bipolar event [174]. The search for the effect of maternal bereavement on neonatal/infant health revealed that loss of a close relative in the 7-12 months before conception did not increase the risks of autism, epilepsy or febrile seizures in the infant. However, loss of a child or spouse in the 6 months preceding conception was positively associated with attention deficit hyperactivity disorder (ADHD) in the male child, childhood obesity and congenital malformation.

Interventions specifically targeting women of reproductive age suffering from a psychiatric condition show that group-counseling [175] and interventions leading to empowerment of women have reported lowering of depression in these women but the results so far have not

been significant (economic skill building: MD -7.53; 95% CI: -17.24, 2.18; counseling: MD-2.92; 95% CI: -13.17, 7.33) [176]. Interventions teaching coping skills or based on stepwise facilitation seem to significantly lower depression levels and these lowered levels were persistent at the 1-yr follow-up [177]. However, morbidities associated with depressions are higher (Figure 8).

Women with serious mental illnesses are at a greater risk of having had >1 sexual partner or having been raped and are hence more likely to have unplanned, unwanted pregnancies [190]. Their support system has been reported to be generally lacking [191]. They have a greater possibility of engaging in risky behavior during pregnancy (substance abuse, suicide attempts) or of being abused [192]. All this makes it imperative for their physicians to not only screen vigorously for such cases but also to provide comprehensive family planning and contraceptive counseling as well as attach them to relevant support systems.

Intimate partner violence

Irrespective of demographics, women around the globe have been subjected to IPV. IPV against women is a major public health concern as it adversely affects both the physical, mental and reproductive health of a woman and that of the newborn. physical abuse by a partner at some point in life was reported by 13–61% of women of 49 years of age and sexual violence by a partner was reported by 6–59% of them [190]. Violence during pregnancy has been associated with poor health outcomes including increased risk of preterm labor [191], antepartum hemorrhage [192], LBW infants [191], fetal loss [193-195], STIs [196] and post-partum depression [197]. Coker et al. [198] reported that women who 'ever experienced' IPV were more than twice as likely to suffer from various kinds of physical and mental health problems. Having experienced IPV is associated with a higher occurrence of unwanted pregnancies [199-201], gynecologic morbidity [202-204] and involvement in risky sexual behaviors [202,204,205]. Data suggests that intensive advocacy interventions may improve the quality of life where as brief advocacy interventions improve safe behaviors [206].

The content of preconception care for women suffering from IPV includes firstly identifying such women, which can be effectively done by asking all women about their experiences of violence from any source, at any point in life. Their condition needs to be evaluated and their injuries treated. Women suffering from IPV need to be informed about the significant harm to the mother, the fetus, and the newborn infant that such abuse can potentially cause and hence of the crucial role of contraceptives. They need be counseled for the psychological trauma that they've suffered from. Finally they need to be referred to an agency/support group that specializes in dealing with such cases. Sexual violence specifically in adolescents is dealt with in the section on ***'Adolescents'*** (Reference to paper on adolescent health).

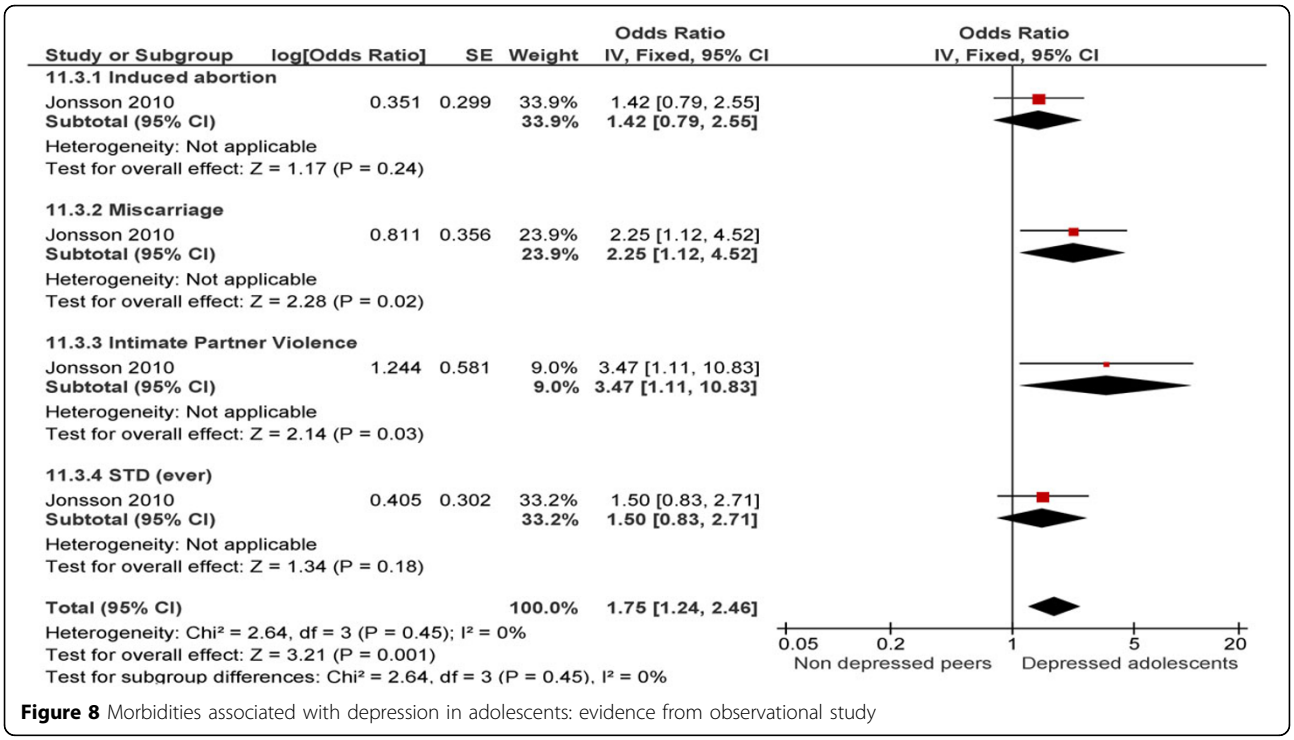

Figure 8 Morbidities associated with depression in adolescents: evidence from observational study

Majority of the reviewed studies on effect of IPV exposure were in women in the general population and were risk aversion studies [191-197,200-205,207-242], while few were intervention studies [176,177,243-253]. From the analysis it was found that IPV positively led to unintended pregnancies (OR 2.33; 95% CI: 1.25-4.34) (Figure 9) [215,218].

No association was found between IPV and condom use in women [196,202,218]. A significant increase in gynecologic morbidities was reported in women suffering from IPV (OR 1.45; 95% CI: 1.13-1.85) [196,203] and rates of STIs were non-significantly raised by around 2 folds in these women (RR 1.89; 95% CI: 0.65-5.47) [202,233]. Gynecologic morbidity increased significantly with any spousal abuse (OR 1.89; 95% CI: 1.23-2.91); combined physical plus sexual violence led to a 72% increase (P 0.04).

With regards to a woman's physical and mental health, IPV had serious detrimental effects in those abused. Ruiz et al. [254] reported that women who had experienced physical, psychological and sexual violence were twice as likely to suffer a chronic disease as those who have not experienced abuse (OR 2.03; 95% CI: 1.18-3.51), especially diseases other than hypertension, diabetes and asthma (OR 2.57; 95% CI 1.38-4.77) [229], and fetal loss [193]. IPV leads to a towering five-fold increase in depression among the victims (P<0.00001) (Figure 10) [222,224] and a two-fold increase in impairment of mental health in the past month only (RR 2.08; 95% CI: 1.70-2.55) [232,233]. Abuse also makes these women 7 times more likely to contemplate suicide [222].

Interventions targeting IPV have mainly looked at behavioral therapies. These studies have yielded non-significant effects on the occurrence of new events of violence post-treatment. A meta-analysis of 4 trials comparing cognitive behavior therapy (CBT) versus no intervention showed a reduction favoring the intervention group [234]. Behavioral couple's therapy, when compared to gender specific treatment, showed greater reductions in post-treatment aggression and recidivism rates, especially multiple couple's group sessions. A dual intervention targeting both IPV and substance abuse showed decreased rates of both in the intervention group (RR 0.71; 95% CI: 0.37-1.38) [188].

Interventions focusing on empowerment of women have been employed to reduce these risks, but their role in decreasing the rate of IPV have so far not been significant. A pilot on the effectiveness of an intervention to reduce male partner reproductive coercion was associated with a large reduction in pregnancy coercion among women who had recently experienced IPV (OR: 0.29; 95% CI: 0.09-0.91) [255].

Discussion

Preconception care (diet and exercise counseling, and a stringent glycemic control) for women with preexisting diabetes is effective in addressing the ever-increasing rates of adverse fetal consequences (congenital malformation, perinatal mortality) as well as serious maternal outcomes (preterm labor, level of maternal HbA1c in the first trimester of pregnancy). This review identified significant impact of preconception diabetic care on reducing congenital malformation and perinatal mortality. This finding is in line with the results of some previous reviews [25,256] with the differences being attributed to inclusion of studies with a low to moderate level of bias. The problem however lies in the fact that a substantial number of women with diabetes do not access such preconception care interventions and continue to have unplanned pregnancies with deleterious MNCH results.

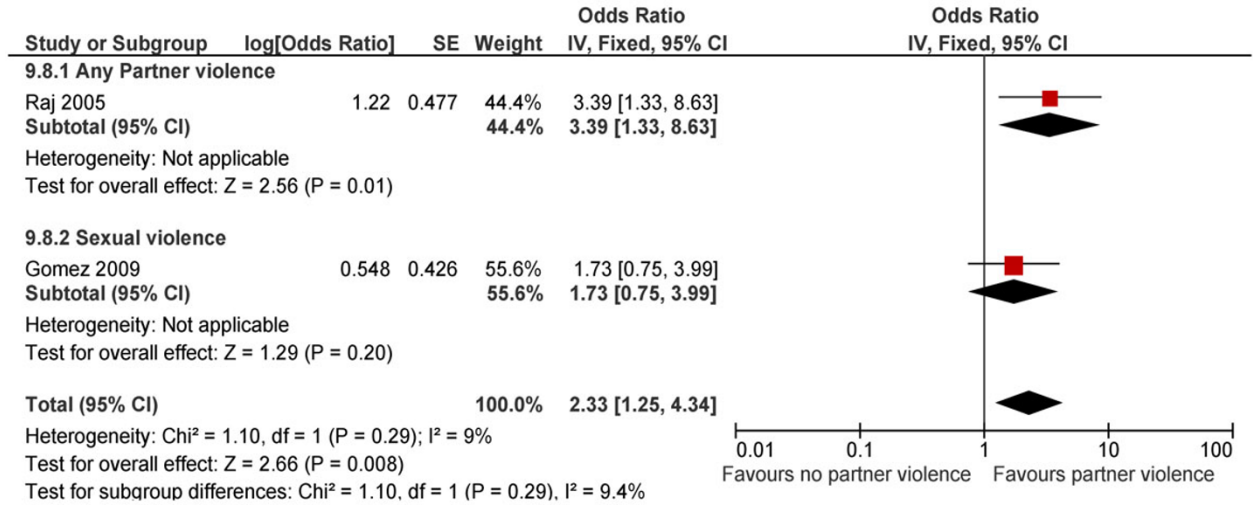

Figure 9 IPV and risk of unintended pregnancies (in women who have undergone IPV in the last 1 year: evidence from observational study

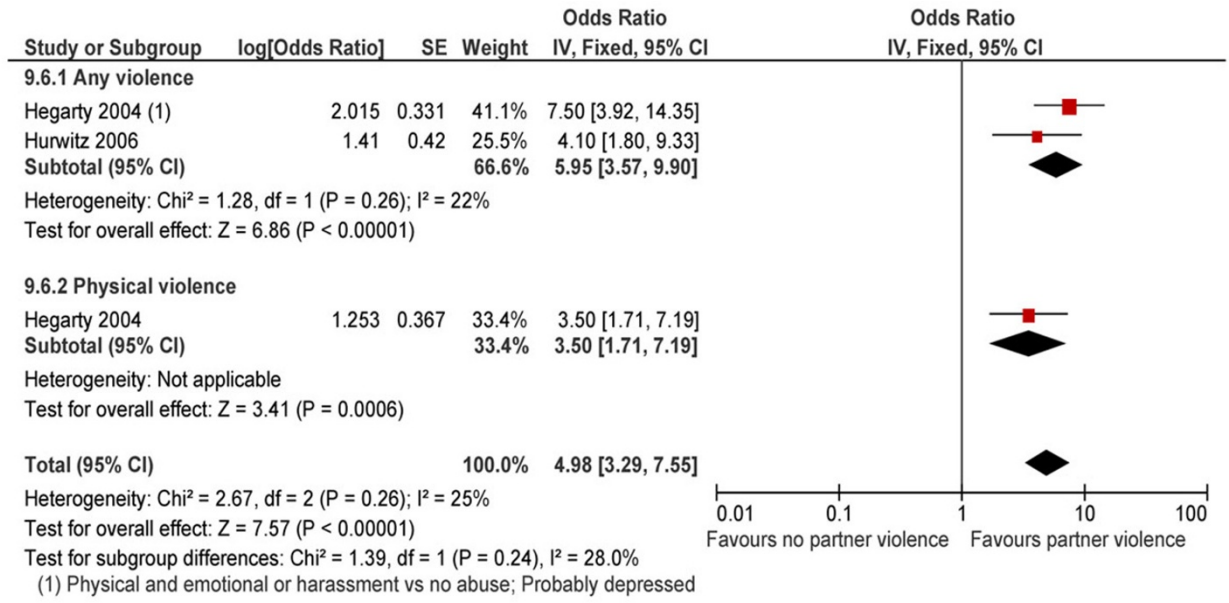

Figure 10 IPV and risk depression (in women who have undergone IPV in the last 1 year: evidence from observational study

Since less than 30% of those with diabetes present for preconception care, every office visit of every female diabetic adolescent or woman of childbearing age should be regarded as a preconception care visit. Also with more women having children in their later years, screening for type 2 diabetes among women of childbearing age becomes more important. Future research, however, needs to aim at evaluating the effectiveness of preconception care on the incidence of other MNCH outcomes like caesarean sections, spontaneous abortions, via proper trials. What it needs more is to find ways of successfully integrating preconception care into the routine care of all women of reproductive age suffering from diabetes.

On the other hand, preconception management is the cornerstone for epilepsy care in women with epilepsy. What is recommended is a multidisciplinary approach, involving the patient's primary care physician, an obstetrician who specializes in high-risk pregnancies, and a neurologist. Women with epilepsy should be reviewed before planning a pregnancy in order to optimize therapy before conception. Ideally changes in antiepileptic drug therapy should be made at least 6 months before planned conception, if possible. All women with epilepsy should be persuaded to begin folic acid supplementation during reproductive years and continue throughout pregnancy. A recent survey [257] reported that women with epilepsy are not getting the advice they need on issues relating to contraception and pregnancy. This point was also conformed in another study [258] which showed that physicians managing women with epilepsy did not place adequate emphasis on preconception care. The current evidence for preconception counseling is encouraging but not conclusive and requires further thorough investigation. Effective elements of counseling or mode of delivery need to be identified via future research. Trials should be conducted to evaluate the value of counseling or other behavioral interventions in the preconception period in reducing clinically relevant outcomes. While there is an extensive support for the pre-conception counseling of all women of child-bearing years suffering from epilepsy, there is a dearth of evidence evaluating the efficiency of such an intervention in dealing with adverse pregnancy outcomes of the disease and its treatment.

Given the complications of the maternal PKU syndrome, a systematic approach to those intending to get pregnant is required. The analysis revealed a significant positive effect of strict dietary control in the preconception period and improved growth parameters in the newborn. Studies have also reported a decrement in other fetal risks associated with the disease after attainment of an adequate control of phenylalanine levels in the 1st trimester, brought about by following a stringent dietary plan before pregnancy. There is evidence that a preconception phenylalanine-restricted diet works, however what is needed now is to finalize a preconception protocol for women with PKU and implement it on a larger scale for better coverage. An absolute dearth of evidence was also identified in women with thyroid dysfunction. However, logic dictates that ensuring maternal biochemical euthyroidism in the first trimester, when the fetus is most responsive tomaternal thyroxine, might optimize fetal outcome. To achieve this target those already suffering from thyroid dysfunction

need to be re-evaluated before they plan to conceive, their treatment regimens need to be re-adjusted and they need to be counseled about the probable risks to both lives that an unachieved euthyroid status may lead to. Future research not only needs to find the missing link between thyroid function before conception and a fall in associated MNCH morbidities, it also needs to focus on how to achieve this in women with thyroid disorders who want to conceive.

Pregnancy is safe in most lupus patients who conceive while the disease is inactive; however pregnancy statistically increases SLE activity. Active SLE prior to pregnancy is associated with a less favourable maternal and fetal outcome and conception should hence be avoided, if possible. The analysis showed that an active disease status in the preconception period significantly increased the risks of gestational flares by 77%, PIH by over three folds, preterm deliveries by twice as much and perinatal mortality by over two-folds. No association was found with pre-eclampsia, fetal growth restriction or spontaneous abortions. These findings highlight the importance of a preconception intervention to address the reproductive issues in women suffering from SLE. Similarly, several drugs used by women with lupus have been contraindicated during pregnancy for their adverse effects on maternal and fetal outcomes.

This review of the literature found important evidence pertaining to the periconception use of certain drugs used regularly for chronic disorders or other purposes. Anti-asthmatics, especially bronchodilator use, in the periconception period led to a more than two-fold increase in the incidence of gastroschisis. Weight-loss drugs led to a 58% increase in the risk of congenital malformations, especially congenital heart defects. OCPs led to a non-significant increase in various pregnancy and fetal outcomes. Vasoactive substances, like aspirin, decongestants and vasoconstrictors were associated with limb defects. It is therefore, advisable to women to take these drugs only when prescribed by doctors after thorough assessment of history and examination of potential side effects.

Mental health conditions are prevalent among women of reproductive age and a substantial proportion goes untreated. Due attention is being paid to screening for and treating psychosocial issues during pregnancy and post-partum but non-pregnant women are being neglected in this regard. There is a deficiency of evidence associating the status of disease and treatment in the preconception period with adverse MNCH effects. This explains the lack of literature on effective interventions targeting such women, implementation of which would be a task of its own. Interventions already proved efficacious in pregnancy should also be evaluated for women before pregnancy. IPV, on the other hand, is a serious, widely prevalent issue. Apart from being violations of human rights, acts of violence profoundly damage the physical, sexual, reproductive, emotional, mental and social well-being of not only individuals but families. IPV has adverse effects on women, leading to an increase in unplanned pregnancies, gynecologic infections and probable fetal loss Current interventions for reducing IPV and related morbidities have mainly looked at behavioral therapies. Behavioral couple's therapy has shown greater reductions in post-treatment aggression and recidivism rates, especially multiple couple's group sessions. Although these interventions may not have shown significant effects yet, there is every reason to believe that thorough outcome evaluations of present programmes along with development of new programs based on sound supposition and identified risk factors will translate into a swift expansion in the near future.

Although the review identified the impact of majority of chronic and mental diseases on MNCH outcomes, it was, however, unable to gather evidence on preconception respiratory diseases such as cystic fibrosis, endocrine problems such as ovarian syndrome and women with cancers. This was mainly because of dearth of literature on these topics particularly from preconception period.

Conclusion

Provision of care to high risk women for chronic medical conditions is as important as any other general health promotion. Delaying and achieving optimal timing of a pregnancy is often an important component of the preconception care of women with medical conditions. Since majority of the pregnancies are unplanned, therefore, reproductive planning and contraceptive considerations for women of reproductive age with chronic medical conditions should be discussed early after diagnosis. IPV is a serious, widely prevalent issue. Apart from being violations of human rights, acts of violence profoundly damage the physical, sexual, reproductive, emotional, mental and social well-being of not only individuals but families. IPV has untoward effects on women, leading to an increase in unplanned pregnancies, gynecologic infections and probable fetal loss. Abuse also leads to grave impairment of the physical and mental health of the victims.

Peer review

review reports are included in additional file 1.

Additional material

Additional file 1: Peer review reports.

Competing interests
We do not have any financial or non-financial competing interests for this review.

Acknowledgment
The publication of these papers and supplement was supported by an unrestricted grant from The Partnership for Maternal, Newborn and Child Health.

Declarations
This article has been published as part of *Reproductive Health* Volume 11 Supplement 2, 2014: Preconception interventions. The full contents of the supplement are available online at http://www.reproductive-health-journal.com/supplements/11/S3. Publication charges for this collection were funded by the Partnership for Maternal, Newborn & Child Health (PMNCH).

Published: 26 September 2014

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doi:10.1186/1742-4755-11-S3-S5
Cite this article as: Lassi *et al.*: Preconception care: screening and management of chronic disease and promoting psychological health. *Reproductive Health* 2014 **11**(Suppl 3):S5.