RBM ONLINE

ELSEVIER

Review

Does preimplantation genetic diagnosis improve reproductive outcome in couples with recurrent pregnancy loss owing to structural chromosomal rearrangement? A systematic review

Mahmoud Iews [a,b], ***Justin Tan*** [a,1], ***Omur Taskin*** [a], ***Sukainah Alfaraj*** [a], ***Faten F AbdelHafez*** [c], ***Ahmed H Abdellah*** [b], ***Mohamed A Bedaiwy*** [a,*]

[a] *Department of Obstetrics and Gynecology, The University of British Columbia, Vancouver, Canada*
[b] *Department of Obstetrics and Gynecology, South Valley University, Egypt*
[c] *Department of Obstetrics and Gynecology, Assiut University, Egypt*

Justin Tan is an Obstetrics and Gynecology Resident at the University of British Columbia. He received his Bachelors in Engineering from the Massachusetts Institute of Technology (MIT), followed by a Masters in Public Health and Biostatistics from the University of Cambridge, and most recently his medical degree from McGill University.

KEY MESSAGE

Despite the purported benefits of preimplantation genetic diagnosis among patients with structural chromosomal rearrangements and a history of recurrent miscarriage, this systematic review demonstrates that natural conception offers similar pregnancy outcomes compared with IVF–PGD. Hence, these patients should be counselled that assisted reproduction technologies should not be offered first-line given the cost and unproven benefits.

A B S T R A C T

Recurrent pregnancy loss (RPL) is a common, yet elusive, complication of pregnancy. Among couples at high risk of RPL, such as those carrying a structural chromosomal rearrangement, preimplantation genetic diagnosis (PGD) has been proposed as a tool to improve live birth rates and reduce the incidence of miscarriage; however, no clear consensus has been reached on its benefits in this population. This systematic review summarizes existing published research on the effect of PGD on pregnancy outcomes among carriers of chromosomal abnormalities with RPL. A comprehensive search of common databases was conducted, which yielded 20 studies. Meta-analysis was precluded owing to significant heterogeneity between studies. The primary outcome of interest was live birth rate (LBR), and a pooled total of 847 couples who conceived naturally had a LBR ranging from 25–71% compared with 26.7–87% among 562 couples who underwent IVF and PGD. Limitations of the study include lack of large comparative or randomized control studies. Patients experiencing RPL with structural chromosomal rearrangement should be counselled that good reproductive outcomes can be achieved through natural conception, and that IVF–PGD should not be offered first-line, given the unproven benefits, additional cost and potential complications associated with assisted reproductive technology.

* Corresponding author.
E-mail address: mohamed.bedaiwy@cw.bc.ca (MA Bedaiwy).
[1] First and second authors contributed equally to the work.

https://doi.org/10.1016/j.rbmo.2018.03.005
1472-6483/

Please cite this article in press as: Mahmoud Iews, Justin Tan, Omur Taskin, Sukainah Alfaraj, Faten F. AbdelHafez, Ahmed H. Abdellah, Mohamed A. Bedaiwy, Does preimplantation genetic diagnosis improve reproductive outcome in couples with recurrent pregnancy loss owing to structural chromosomal rearrangement? A systematic review, Reproductive BioMedicine Online (2018), doi: 10.1016/j.rbmo.2018.03.005

Introduction

Human reproduction is an intricate process that requires a synchronous dialogue between a myriad of genetic, anatomic and environmental factors. Naturally, this results in frequent errors, with an estimated 15–25% of human conceptions failing to achieve viability and resulting in early pregnancy loss (El Hachem et al., 2017). As an extension, recurrent pregnancy loss (RPL) is a distinct disorder defined by two or more failed clinical pregnancies and affects 2–5% of couples (Practice Committee of the American Society for Reproductive Medicine, 2012). Among many different causes, structural chromosomal rearrangements substantially increase the incidence of RPL and ultimately contribute to a significant cause of physical and psychological distress. Consequently, significant efforts are being made to improve treatment modalities, reduce the risk of miscarriage and decrease the time needed to achieve a successful pregnancy among carriers of structural chromosome rearrangements (Zidi-Jrah et al., 2015).

Epidemiologic and pathologic studies suggest that structural chromosomal rearrangements, such as reciprocal and Robertsonian translocations, contribute to 3–4% of cases of RPL (De Braekeleer and Dao, 1990). Hence, among known carriers of chromosomal abnormalities, technologies such as preimplantation genetic diagnosis (PGD) to screen and prevent the transfer of genetically inherited unbalanced embryos have been shown in several small observational studies to improve live birth rates (LBR) and reduce the incidence of unfavourable sequelae such as miscarriage (Munne et al., 1998; Munné et al., 2000). More recent prospective studies (Franssen et al., 2011; Platteau et al., 2005) and a prior systematic review (Hirshfeld-Cytron et al., 2011), however, found no overall differences in LBR compared with natural conception. In addition, a cost-analysis by Murugappan et al. (2015) provided insight into the significant cost differences between IVF–PGD and expectant management despite similar pregnancy outcomes in women with unexplained RPL of whom one of the partners is a carrier of a structural chromosomal rearrangement. Hence, given the invasive and costly nature of IVF–PGD, as well as potential complications associated with ovarian stimulation, the value of such a procedure is less clear.

No clear evidence-based consensus has been reached on whether the benefits of PGD outweigh the costs among couples with known structural chromosomal rearrangement and a history of recurrent pregnancy loss. This is because results are conflicting and well-controlled prospective studies are lacking.

To further elucidate the evidence in support of and against the routine use of PGD in this population group, we systematically reviewed the literature on live birth and miscarriage rates among known carriers of structural chromosomal rearrangement with a history of RPL.

Materials and methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Liberati et al., 2009).

Search strategy and allocation of studies

We systematically searched the following electronic databases: *EMBASE* (Ovid), *MEDLINE* (Ovid), *Cochrane Central Register of Controlled Trials* and *Grey Literature Database* from inception to July 2017, as well as the reference lists of the selected articles.

We used the following search terms in each of the databases: 'recurrent or repeated or habitual or pregnancy loss or miscarriage or spontaneous abortion or fetus wastage, combined with translocation, reciprocal translocation, Robertsonian translocation, Inversion, chromosomal structural rearrangement or abnormality or aberration or preimplantation genetic diagnosis'.

Eligibility criteria and data extraction

All randomized, non-randomized and cohort studies that reported reproductive outcome after natural conception or PGD for structural chromosomal rearrangement in couples with a history of recurrent pregnancy loss were reviewed. In this case, RPL was defined as a history of two or more clinical pregnancy losses at less than 20 weeks' gestation. Additional studies were extracted from the references in the full-text articles. Articles were restricted to English language only. We also considered published abstracts from conferences but excluded review articles, case reports and case series.

Studies were grouped according to three categories: studies dealing with medical management or natural conception only; studies dealing with PGD only; and studies comparing natural conception and PGD.

Two reviewers (MI and SA) independently searched and reviewed the retrieved articles and results were compared. Any disagreement was resolved by discussion. The final decision was taken by the senior investigator (MB).

The primary outcome of interest was live birth rate per couple, defined as the percentage of couples achieving a live birth after 24 weeks' gestation. Secondary outcomes of interest included miscarriage rate per couple and time to successful pregnancy.

Results

A flow chart of the search strategy and studies included in our systematic review is presented in **Figure 1**. Most of the studies were retrospective and case-controlled. Unfortunately, there were no randomized controlled trials (RCT), but two comparative studies were identified, one of which was an abstract. A search of studies describing reproductive outcomes after natural conception and IVF with PGD resulted in 285 publications. After rejecting articles that did not address our research question, 20 studies were included for our analysis. Specifically, 10 studies evaluated reproductive outcomes after natural conception, eight studies after IVF and PGD, and two studies directly compared differences in live birth rates between couples conceiving naturally compared with after IVF and PGD. (**Figure 2**)

Reproductive outcomes after natural conception

A detailed summary of the 10 studies that investigated reproductive outcomes after attempted natural conception among couples with a known chromosome rearrangement and a history of recurrent pregnancy loss is presented in **Table 1** (Carp et al., 2004; Desjardins and Stephenson, 2012; Dong et al., 2014; Flynn et al., 2014; Franssen et al., 2006; Kabessa et al., 2017; Kochhar and Ghosh, 2013; Pal et al., 2009;

Please cite this article in press as: Mahmoud Iews, Justin Tan, Omur Taskin, Sukainah Alfaraj, Faten F. AbdelHafez, Ahmed H. Abdellah, Mohamed A. Bedaiwy, Does preimplantation genetic diagnosis improve reproductive outcome in couples with recurrent pregnancy loss owing to structural chromosomal rearrangement? A systematic review, Reproductive BioMedicine Online (2018), doi: 10.1016/j.rbmo.2018.03.005