Reproductive BioMedicine Online (2016) ■■, ■■–■■

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REVIEW

Pregnancy complications in spontaneous and assisted conceptions of women with infertility and subfertility factors. A comprehensive review

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Abstract In the literature, there is growing evidence that assisted reproductive techniques increase the risk of pregnancy complications in subfertile couples. Moreover, many concomitant preconception risk factors for subfertility are frequently present in the same subject and increase the risk of pregnancy complications. This review aimed to summarize in a systematic fashion the best current evidence regarding the effects of preconception maternal factors on maternal and neonatal outcomes. A literature search up to March 2016 was performed in IBSS, SocINDEX, Institute for Scientific Information, PubMed, Web of Science and Google Scholar. An evidence-based hierarchy was used to determine which articles to include and analyse. Available data show that the risk of pregnancy complications in spontaneous and assisted conceptions is likely multifactorial, and the magnitude of this risk is probably very different according specific subgroups of patients. Notwithstanding the only moderate level and quality of the available evidence, available data suggest that the presence and the treatment of specific preconception cofactors of subfertility should be always taken into account both in clinical practice and for scientific purposes.

KEYWORDS: complications, infertility, obstetric, pregnancy, subfertility

http://dx.doi.org/10.1016/j.rbmo.2016.08.007
1472-6483/

Please cite this article in press as: Stefano Palomba, Susanna Santagni, Karen Gibbins, Giovanni Battista La Sala, Robert M. Silver, Pregnancy complications in spontaneous and assisted conceptions of women with infertility and subfertility factors. A comprehensive review, Reproductive BioMedicine Online (2016), doi: 10.1016/j.rbmo.2016.08.007

Introduction

Many investigations note increased risks of obstetric and/or neonatal complications in infertile patients or when pregnancy is achieved after medical or surgical treatment for enhancing fertility (Barnhart, 2013). The Centres for Diseases Control and Prevention (CDC) report on assisted reproductive techniques surveillance states that assisted reproductive procedures are associated with potential risks to the mother and fetus (Sunderam et al., 2015). However, available data are heterogeneous and complex because infertile couples often have preconception comorbid and potentially unrecognized risk factors for subfertility, and the underlying risk factors that lead to infertility may also lead to pregnancy complications and long-term maternal and offspring health problems. Multiple maternal factors associated with infertility may contribute to the adverse outcomes rather than the assisted reproductive procedures themselves (Hayashi et al., 2012). In fact, data adjusted for maternal age, parity, prepregnancy height and weight, smoking, alcohol consumption and pre-existing medical and gynaecologic diseases, revealed no difference in obstetric and/or neonatal complication rates among 242,715 women with singleton pregnancies that received different treatments for infertility (Hayashi et al., 2012). Thus, a substantial proportion of the increased risks in assisted reproductive techniques singleton pregnancies can be attributed to parental characteristics (Pinborg et al., 2013). A growing number of studies have shown that reproductive disorders can per se induce an increased risk of pregnancy complications with similar mechanism of action (Vannuccini et al., 2016). This is true for systemic diseases, such as obesity or polycystic ovary syndrome (PCOS), and for gynaecological conditions, such as uterine fibroids and polyps and endometriosis/adenomyosis.

Another difficulty is to distinguish the contribution of specific reproductive disorders or infertility/subfertility to poor pregnancy outcomes (regardless of fertility treatment) (Talaulikar and Arulkumaran, 2012) because reproductive disorders rarely occur alone (Holoch et al., 2014). The treatment of one or more subfertility factors before natural or assisted conception may be another crucial confounder influencing the pregnancy and neonatal outcomes. Thus, the overall obstetric risk includes the woman's characteristics and genetics, obstetric risks such as twins, and finally the potential impact of each element of assisted reproductive techniques.

Although meta-analyses and population-based studies have been conducted on the obstetric risks of infertility/subfertility and its treatments, there was no single comprehensive systematic review on the impact of subfertility and reproductive disorders on pregnancy outcomes independently from the use of assisted reproductive techniques. Thus, the aim of the current study was to review comprehensively and in a systematic fashion available evidence regarding the effects of preconception maternal factors on maternal and neonatal outcomes in spontaneous and assisted conceptions.

Materials and methods

Multiple strategies were used to search and identify relevant demographic, epidemiological, clinical and experimental studies. Sociological online libraries (IBSS, SocINDEX), Institute for Scientific Information, PubMed, Web of Science and Google Scholar were consulted. Only articles written in English were considered. Studies available up to March 2016, and reporting data about the relationship between obstetric and neonatal complications and conditions related to subfertility/infertility and their treatments were included.

Additional journal articles were identified from the bibliography of the studies initially included. Literature searches and abstract screening were performed by two researchers (SP and SS).

An evidence-based hierarchy was used to determine which articles were included. The study included meta-analyses for each specific issue, and updated them with more recent clinical studies. A priority was given for randomized controlled trials (RCT). Moreover, nonrandomized prospective, uncontrolled prospective, retrospective and finally experimental studies were considered sequentially. In cases when specific data for infertile patients were unavailable, data was reported from the general populations to provide a frame of reference. Any disagreement or uncertainty was resolved by discussion to reach a consensus.

An attempt to summarize the available best evidence about the relationships between each subfertility factor and main adverse obstetric and neonatal outcome was performed. Level and quality of evidence for each relationship was assessed. The level of evidence was evaluated according to The Oxford Centre for Evidence-Based Medicine (OCEM)–Levels of Evidence 2011 guidelines (2011) (http://www.cebm.net/index.aspx?o=5653). The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Guyatt et al., 2011).

Infertility

Infertility is usually defined as the failure to achieve a clinically detectable pregnancy after more than 12 months of regular unprotected intercourses (the time to pregnancy [TTP] longer than 12 months) (Boivin et al., 2007). It is common, affecting at least one out of six couples (Boivin et al., 2007). Irrespective of the cause of infertility, the TTP is an important factor influencing the risk of pregnancy complications after conception. Saunders et al. (1988) first reported that infertility is an independent risk factor for subsequent problems during pregnancy. Subsequently, many studies suggested that infertility itself, regardless of treatment, is associated with an elevated risk of adverse pregnancy outcome. As infertility is a heterogeneous condition, it is possible that some of the mechanisms leading to infertility also play a role in the aetiology of these adverse outcomes.

A systematic review with meta-analysis (Messerlian et al., 2013) analysed the effect of TTP of more than 12 months on pregnancy and neonatal complications. The study included a total sample size of 1,269,758 births, including 19,983 in the exposed/infertile group and 1,249,775 in the unexposed/fertile group, and 68,885 preterm births (PTB). When only five studies including matched or stratified participants were analysed, pregnancies with TTP longer than 12 months had an odds ratio (OR) of 1.39 (95% confidence interval [CI] 1.20 to 1.62) for PTB. If the eight studies where regression models were used are pooled, the result was modestly attenuated

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