Combined low dose aspirin and steroids vs. placebo in management of patients with unexplained recurrent miscarriage: Randomized clinical trial

Thesis

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INTRODUCTION

Recurrent pregnancy loss (RPL) is defined as at least two or three sequential abortions before the 20th week of gestation. RPL occurs in 1% to 5% of all pregnancies. Despite the fact that several factors such as environmental and stress factors, chromosomal abnormalities, coagulation protein defects and, endocrine, anatomical and autoimmune disorders are involved in approximately 60% of RPLs, in the remaining 40% of the cases, the etiology of abortion is unknown and is classified as unexplained RPL (URPL) ***(Gharesi-Fard et al., 2014).***

Fifty percent of RPL are caused by anatomical, immunological, genetics, endocrine, thrombophilic and environmental factors. However, in 50% of the cases, the cause of abortion is unknown or idiopathic ***(Shakarami et al., 2015).***

Recurrent pregnancy loss (RPL) is a significant health problem, affecting 5% females of reproductive age. Women at reproductive age face significant economical, emotional and social problems due to RPL ***(Kashif et al., 2015).***

Established and suggested risk factors for recurrent miscarriage are increasing number of successive previous pregnancy losses ***(Clifford et al., 1997)***, parental chromosomal anomalies, maternal thrombophilia disorders, and structural uterine anomalies. Finally, increasing maternal age is accepted as the most important risk factor for future miscarriage both in women with recurrent miscarriages ***(Clifford et al., 1997)*** and in the general population ***(Nybo Andersen et al., 2000).***

About 50% of Recurrent pregnancy loss cases still remain unexplained, or idiopathic. In this group of patients, fetal chromosomal abnormalities have been reported to be the most common cause of recurrent pregnancy loss, accounting for up to 55% of cases, thus leaving a remainder of 24.5% of truly unexplained recurrent pregnancy loss ***(Sugiura-Ogasawara et al 2012).***

Although progesterone appears to be the main factor initiating decidualization. A number of other factors including cytokines appear to facilitate this event. Failure in either the early blastocyst endometrial dialogue or decidualization may lead to implantation or pregnancy failure, alteration in the expression of a number of factors thought to contribute to the

embryo/ endometrial dialogue have been shown at this time in endometrium from women with recurrent miscarriage ***(Li et al., 2002)***.

The concentrations of different endometrial leukocytes have therefore been investigated in a number of studies to find links to the development of miscarriages ***(Quenby et al., 1999).***

We performed this study on women who presented with unexplained recurrent to explore the efficacy of low dose aspirin and steroids in the management of such cases.

AIM OF THE WORK

The aim of this study is to assess the efficacy of low dose aspirin and steroids therapy in the management of women with recurrent miscarriage

Research Hypothesis:

Women with recurrent unexplained miscarriage, can be treated with low dose aspirin and steroids.

Research Questions:

In women with recurrent unexplained miscarriage, can treatment with low dose aspirin and steroids be effective?

Primary outcome:

- Completion of 20weeks gestation.

Secondary outcome:

- Live birth rate.

Chapter (1)

Recurrent Early Pregnancy Loss (Miscarriage)

Definition:

Miscarriage is the commonest complication of pregnancy. The generally accepted definition stipulates that the fetus or embryo should weigh 500gm or less, a stage nonexpanding to a gestational age of 20 weeks, according to the world health organization ***(Kolte et al., 2014).***

A preclinical miscarriage is defined as a demise which occurred before 6 weeks of gestation. Clinical miscarriage can be divided into embryonic or fetal: embryonic miscarriage is defined as an embryo with crown rump length of more than or equal to 5 mm; without cardiac activity. A fetal miscarriage is defined as a fetus of 10-20 weeks size without cardiac activity ***(Rai and Regan, 2006; Stephenson and Kutteh, 2007)***.

However, there is no consensus regarding the definition of recurrent miscarriage and many clinicians define recurrent miscarriage as two or more losses before the fetus has reached

viability ***(Zidi-Jrah et al., 2016)***. The number of miscarriages has been a debate, according to the Royal College of Obstetricians and Gynecologists, the definition is three or more consecutive losses ***(RCOG guidelines, 2003),*** the American Society for Reproductive Medicine ***(ASRM, 2012),*** the definition is two or three consecutive losses.

The definition variation from three consecutive losses to two consecutive losses made an increase in the scale of the problem from 1% to 5% of all couples trying to conceive ***(Greenwold and Jauniaux, 2002)***.

Incidence:

Preclinical or very early pregnancy loss as it is sometimes referred to, is seen in 31 % of patients ***(Shakarami et al., 2015).*** This entity is diagnosed by performing serum beta HCG assays in the late luteal phase prior to the onset of the next cycle. This accounts for the reduced fecundity of the human female to 30-40% observed in IVF cycles. This also explains the biochemical pregnancies encountered after assisted reproductive techniques ***(Farquharson et al., 2005)***.

About 15% of couples lose one recognized pregnancy and 2% lose two. The theoretical risk of three or more losses is only 0.34% ***(Carlos et al., 2001; Kiwi, 2006)***.

Women with a history of one miscarriage carry a 24% risk of miscarriage in the next pregnancy, while women with a history of previous 2 miscarriages carry a 26% risk and those with history of previous 3 miscarriages carry a 32% risk of recurrence and thus women who had miscarried two or more consecutive pregnancies deserve an evaluation to look for the cause, which sometimes can be treated ***(Carlos et al., 2001; Kiwi, 2006)***.

Epidemiological Parameters Relevant for Recurrent Pregnancy Loss Occurrence

Using the traditional definition, the incidence of RPL is the number of new women each year (or in another defined period) suffering their third consecutive pregnancy loss, and the prevalence of RPL is the number of women in a population who, at a specific time point, have had three or more consecutive pregnancy losses. The incidence /prevalence is often expressed as a rate of those individuals being at risk for the disorder. The number in the denominator

could be all women in the population, women of fertile age or women who had attempted pregnancy at least two or three times. Indeed, the estimate of the incidence/prevalence of RPL is very uncertain since in most countries there is no nationwide registration of miscarriages or RPL, and many early miscarriages will not be treated in hospitals and are thus not registered ***(Kumar et. al. 2011).***

There is no valid estimate of the incidence of RPL whereas there are a few estimates of the prevalence rate of RPL. Alberman E.et al 1988. Whoever Kirsten Duckitt etal2011 said that it affects 1% to 2% of women, half of whom have no identifiable cause. Overall, 75% of affected women will have a successful subsequent pregnancy, but this rate falls for older mothers and with increasing number of miscarriages. Antiphospholipid syndrome, with anticardiolipin or lupus anticoagulant antibodies, is present in 15% of women with recurrent first and second trimester miscarriage *(**Bradley et. al. 2002**).*

Number of Previous Miscarriages

Almost all prospective studies of RPL patients show remarkable consistency in finding an increasing risk of miscarriage as the number of previous miscarriages

increases. The prognostical negative effect of the number of previous miscarriages could, in theory, be attributed to the fact that maternal age and the presence of age-related risk factors for miscarriages are positively correlated to gravidity. However, in multivariate analyses of clinical and Para clinical parameters of potentially prognostical impact in RPL, the number of previous miscarriages has without exception remained the strongest prognostical parameter also after adjustment for other risk factors ***(Matovina et al., 2004).***

Maternal Age

The age of women with RPL will influence the findings in studies of endocrinological and nongenetic immunological biomarkers. With progressing age the ovarian reserve will diminish and, both during pregnancy and in the nonpregnant state, secretion of ovarian steroid hormones will be reduced. Immune parameters such as production of autoantibodies and T helper 2 cytokines are affected both directly by increased maternal age but also indirectly through diminished secretion of ovarian steroids. It seems that the impact of age on miscarriage rate in RPL is quite modest