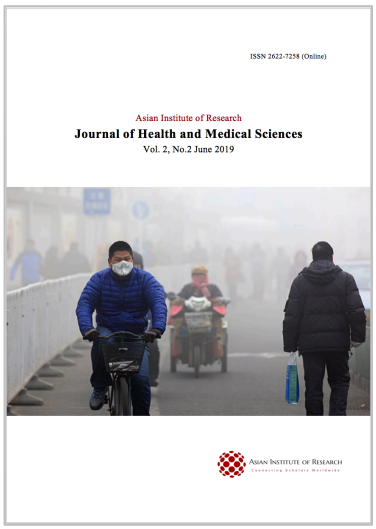

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Using an IVF Population to Examine Gestational Age Patterns in Early Miscarriage

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Abstract
The lengths of gestation of 68 confirmed miscarriages from an in vitro fertilization (IVF) program were compared to expected gestational ages from the literature in order to elucidate patterns of early, undiagnosed miscarriages. The peak frequency of miscarriages in the IVF group was earlier than expected, suggesting that the rate of early miscarriage in the general population might be underestimated.

Keywords: Gestation, IVF, Miscarriage, Spontaneous Abortion

INTRODUCTION

The incidence of spontaneous abortion has commonly been quoted as anything from 9-10% of all pregnancies (Tietze, 1953; Tong et al, 2008) to 20% (Merck Manual, 2019) and above (García-Enguídanos et al, 2002), though the probability of an event seems to decline with advancing gestational age (Tong et al, 2008). There are differences in etiology between early miscarriages, defined as those occurring before the 12th week of pregnancy, and late miscarriages (Kallen, 1988). It seems that the majority of early miscarriages display gross chromosomal anomalies, perhaps explained as a maternal immunologic response in a natural selection paradigm (Warburton et al, 1980). Late miscarriages, on the other hand, have a host of causes, from disease to injury (Regan & Rai, 2000).

It is possible that oft cited statistics, while including induced or surgical abortions, do not include many early unrecognized abortions, since these often go unreported or indeed unrealized, more commonly experienced and dismissed as heavy periods. To this way of thinking, common statistics would underestimate the incidence of early miscarriage in the general population. In seeming support of this hypothesis, after examining the morphology of embryos recovered after hysterectomies, Hertig et al (Hertig et al, 1944) suggested a rate of 28.6% for early miscarriages, thus pushing the overall rate of spontaneous abortion to over 50% of all pregnancies. This high estimate is shared by others, who suggest that half of all zygotes spontaneously fail (Cunningham et al, 2013).

Infertility programs provide a valuable opportunity to observe pregnancies from the point of conception to their eventual outcomes, thus providing a window into a stage of fetal development that is typically unrecognized or unmonitored in the naturally conceiving population (Shoham &Zosmer, 1991). Among pregnancies achieved after difficulties in conceiving, the reported miscarriage rate is typically higher, in part because such pregnancies are more closely monitored. For instance, Wang et al (2004) computed a relative risk of 1.20 (1.03, 1.46) in the assisted reproduction population, relative to the naturally conceiving population. Shoham et al (1991) point out

that such figures lead to the impression that infertility patients have an actual higher incidence of spontaneous abortion than the so-called "spontaneously conceiving" population, when the disparity may in fact be a data artefact caused by the lack of a suitable control group that is as closely monitored.

Some types of infertility treatment might actually counter tendencies toward miscarriage. Balasch et al (1996) investigated the use of IVF (in vitro fertilization) as a treatment for women who have experienced unexplained recurrent miscarriages. In their pilot study, their interpretation was that the IVF process somehow avoided or negated the physiological process that was causing spontaneous abortions in those women. Since immunological aberrations have been proposed as the commonest cause of unexplained fetal losses (Hill, 1992), Balasch et al (1996) suggested that their findings were explained by the implantation of several embryos, as is the typical IVF methodology, thus encouraging the maternal immune system to actively support the pregnancy by favouring the recognition of fetal antigens.

To add further empirical data to the discussion of the true incidence of early miscarriage, the present study was undertaken. We examined the experiences of a closely monitored IVF population to observe the timing of spontaneous abortion in a small clinical set.

METHODS

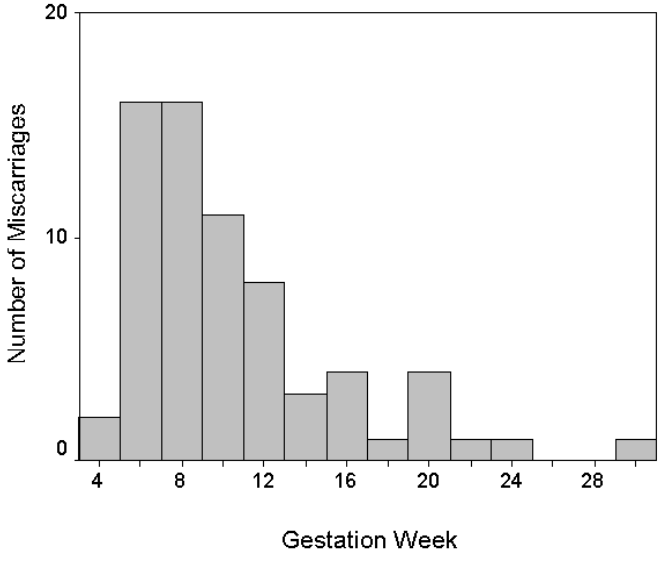
As part of a larger, unrelated study (Deonandan et al, 2000), 191 random patient files from between 1992 and 1997 were examined at a Canadian IVF clinic. Incidences and details of confirmed miscarriage were noted, with their lengths of gestation analysed descriptively and graphically.

RESULTS

Of the 191 patient files examined, 68 were found to have experienced spontaneous abortion. Karyotypic data were available on 10 of the 68 subjects; chromosomal anomalies were present in 5 of these. Thus, the prevalence of chromosomal anomalies in cases of early miscarriage is difficult to assess in these data, but is apparently not high. Indeed, the clinical procedure for selecting appropriate gametes for combination is typically one that tries to maximize eventual zygote robustness.

The frequency distribution of gestational ages for these 68 miscarriages is presented in Figure 1. The steepest attrition rate occurs from the gestational age of 4 weeks to 12 weeks; the majority of losses were reported in that age range.

Figure 1- Pregnancy Week Distribution in 68 IVF Miscarriages



DISCUSSION

In these data, the peak frequency of miscarriages was greatest at 8 weeks gestational age. This is earlier than the peak of 9-13 weeks reported by Kallen (1988) based on the distribution of gestational ages for 610 presumably non-IVF related miscarriages in a given hospital. It is also an earlier peak than that reported by Mukherjee et al (2013), who found a rate of 2-4% in the general population for pregnancies at 8-13 weeks.

The Kallen and Mukherjee data described general populations, whereas the present data arise from IVF clinical patients. Thus, the samples may not be comparable in terms of miscarriage risk. However, it is most likely that the major difference between the clinical and general population samples is in the extent of pregnancy detection. For the general population, only outcomes of detected pregnancies are known. It has been suspected that very early miscarriage is under-detected and under-reported (Kallen, 1988) and our data would support that suggestion. In addition to skewing the gestational age distribution of miscarriages, such under-detection would also result in under-estimation of miscarriage rates. The value of an IVF population in this exploration is that each attempt at pregnancy is closely monitored, so undetected pregnancies (and hence undetected miscarriages) are unlikely.

Epidemiological miscarriage data are flawed by a lack of consistency in reporting gestational age (Santee & Henshaw, 1992). For example, pregnancy can be measured from the beginning of last menstruation or from fertilization, which is 14 days after the 1st day of the last menstrual period (Santee & Henshaw, 1992). Hence, there is significant data quality value in closely monitoring a particular clinical population whose reproductive enterprise is transparent. The challenge is finding such a group that is representative of the general population, and not of an etiology suggestive of impaired reproduction, as is our IVF population.

One approach is to consider a larger sample size of IVF (or otherwise closely monitored) pregnancies, to more convincingly compare to the spontaneously conceiving population. Concerns for the supposed fragility of IVF embryo implantations may be alleviated by consulting a population of less severe fertility impairment, such as fecund women utilizing donor sperm in unstimulated non-IVF cycles for cases of male-factor infertility. Such a group would more closely resemble the reproductive profile of the general population.

CONCLUSION

Miscarriage may occur more commonly than generally reported and there may be a higher proportion of miscarriages occurring before 8-12 weeks gestational age.

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