

Coronavirus Disease 2019: A Comprehensive Review on Recent Clinical Updates and Management Tools for Pharmacists

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ABSTRACT

Objective: In the recent years, the ratio of pregnancy has increased at advanced maternal age (AMA) in comparison to the previous times where giving birth was common around age 18. The purpose of this review paper is to develop a comparative study of demographic and obstetric properties of primiparous females at young and advanced maternal age.

Methods: A cross sectional study was carried out of the participants based upon the inclusion strategy. Two groups with 150 participants in each was made; one group had participants aged above 35 years and other group had participants with age between 20 to 29 years. Variables including weight, BMI, age, pre-pregnancy condition, health state, financial status and other factors were also included.

Results: It was found that females with advanced age were more financially stable, literate, and professionals

who pursued their carriers even after bearing a child. These advanced age women also reflected more developed background knowledge about pregnancy, child care, labor and parental attitude. However, medically speaking, these females faced more infertility issues, miscarriages and Caesarean sections in comparison to young primiparous females.

Conclusion: Pregnant ladies of advanced maternal age were different from young ladies in knowledge, demographic, financial, and parental attitudes and characteristics.

Key words: *In Vitro* fertilization, Recurrent implantation failure, IL-1; IL-10, Interferon, Thin endometrium

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INTRODUCTION

With the passage of time maternal age has been increased across the globe. In the developed countries the fertility rate of women with age more than 35 is growing rapidly. A study conducted in Australia has stated that fertility has surpassed of women aged 35-39 years as compared to women with age 20-24 years (Australian Bureau of Statistics, 2018; Hamilton BE, et al., 2009). In the United States, the birth rate for women aged 35 to 39 years increased to 47.5 births per 1000 women in 2007, the highest rate since 1964, and the birth rate for women aged 40 to 44 years increased to 9.5 births per 1000 women in 2007, the highest rate since 1968. Correspondingly, the live birth rate for women aged 40 to 44 years increased by 43% (from 4.2 to 6.0 per 1000 females), and the live birth rate for women aged 45 to 49 years increased by 59% (from 0.17 to 0.27 per 1000 females). Childbearing at an older age is becoming more common while delayed childbearing has become socially acceptable (PHAC, 2018). Many contributing factors are major reason of delaying child birth in mid-thirties. Women are now much more conscious about valuing some other important factors such as independence through education, secure employment, and financial stability than women who had their children earlier in life therefore they opt delayed childbearing (Benzies K, et al., 2006). A study conducted by Tough et al. has stated that four main factors are considered for delayed childbearing such as: Financial security, their partner's suitability to parent, their own interest in or desire for having children, and their partner's interest in or desire for having children (Tough S, et al., 2007).

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Multiple pregnancy complications and adverse outcomes are linked with pregnancies in advanced maternal age as compared to younger ages (Usta IM and Nassar AH, 2008). In the developed countries there is an increase in the overall maternal mortality rate associated with increasing maternal age. In UK according to the Confidential Enquiries into Maternal Mortality the major cause of maternal death from 1994 to 1996 among all ages were thrombosis and hypertension.

While death as a result of thrombosis did not appear to be related to increasing maternal age, death as a result of hypertension was five times more likely in women aged ≥ 40 years than in women aged ≤ 25 years. From 1997 to 2000, women aged 35 to 39 years had a five-fold higher risk of maternal mortality than women aged 20 to 24 years (Wang FT and Beski S, 2002). Furthermore, several studies have demonstrated an association between AMA and preterm birth, low birth weight, stillbirth, chromosomal abnormalities, gestational diabetes, multiple births, and higher rates of Caesarean section (Delpisheh A, et al., 2008). AMA is also associated with increasing health care use and costs in relation to childbirth because of higher rates of Caesarean section, screening and diagnostic tests, infant mortality, and longer hospital stay. Although a postponed pregnancy may be risky for the mother and her foetus, the exact mechanisms underlying these greater risks for adverse pregnancy outcomes among women of AMA are not well understood (Hansen JP, 1986). Some investigators have identified maternal characteristics as determinants of maternal morbidity and obstetric interventions. Recent trends in maternal characteristics such as increasing maternal age and pre-pregnancy weight have increased the risk factors for labour induction and Caesarean section. For instance, the increase in primary Caesarean section rates has been identified as a consequence of changes in maternal characteristics such as age, parity, and weight. Because of the growing number of women who are delaying pregnancies to later in life (Temmerman M, et al., 2004), it is important to understand the characteristics of these women in comparison with younger women at a population level. This knowledge will facilitate the development of strategies for reducing modifiable risk characteristics (Swiet de M, 2000; Rusen ID and Liston R, 2004). The purpose of this study was to compare demographic characteristics and obstetric characteristics outcomes of primiparous women aged ≥ 35 years (Jane CG, et al., 2005).

LITERATURE REVIEW

Background

Fertility has a relation with age and it keeps on changing. With the beginning of puberty, both males and females enter their fertile zone. Menstruation and ovulation in females are known as the signs of puberty. On the basis of this, when menopause arrives, females are no longer able to conceive. Generally, the fertility potential gets lower with the increase in age; and in some cases it ends almost 5 to 10 years before the arrival of menopause.

In the present time, females all around the globe usually prefer to start their families in their early 30s, this is giving rise to age-related infertility issues. No doubt, women today are healthier, better educated and stable than the females from the past, but this does not cop up with the nature's cycle of declining fertility potential with age. Therefore, it is imperative to understand the difference between advanced maternal age females and young females on the basis of their obstetric characteristics because the number of eggs also decreases with age (Huang L, et al., 2018).

Ovulation and the menstrual cycle

Women, during their reproductive years, get the menstrual blood every month because they ovulate regularly. Eggs mature inside the follicles which are fluid filled sphere like structures. When each menstrual cycle begins, the time when period starts, a gland in brain known as the pituitary gland produces a hormone. This hormone is known as follicle stimulating hormone (FSH) that triggers the rapid growth of follicles on both the ovaries.

Under normal conditions, only one out of many follicles reach the maturity stage and ovulate by releasing an egg while rest of them simply degenerate after stopping their further growth. A lady gets pregnant when the egg is fertilized and implants in endometrium (inner lining of uterus). However, if pregnancy does not occur then the uterus shed the inner lining of itself as the menstrual blood and the cycle continues. At the onset of puberty, females often have irregular menstrual periods owing to irregular ovulation, but this usually gets settled by the age 16 and regular period cycle is established. A female's cycle is between 26 to 35 days and when she reaches her late 30s to early 40s, she began to experience irregularities. The cycle gets shorter and she often skips menstrual periods as her body begin to skip ovulation. Ultimately, the menstruation cycle completely stops and when the time of about one year passes by with no periods, then it is said to be the stage of menopause. Changes occur in ovaries with age. Unlike men, who produce sperms throughout their lives and there is no such thing like menopause for them, a female is born with follicles containing all the eggs in her ovaries. When a female is born, she has over one million follicles which drop down to 300,000 at the onset of puberty. During her reproductive years, about 300 follicles are ovulated. Rest of the other follicles degenerate through a process known as atresia. Atresia continues despite any condition of the female like either she is pregnant or having periods, using contraceptive pills or going through some infertility medication.

Fertility in aging females

The finest reproductive years of a female is in her 20s, it began to decline in 30s, especially after 35 years of age. When a comparison is made between the young and advanced age female, it was found that a healthy female in her 20s has 35% chances of getting pregnant and 30 plus year woman has 20% chances of conceiving (Jacobsson B, et al., 2004). This percentage means that for every 100 fertile 30 years old women, only 20 out of 100 will conceive and rest of the 80 have to try again for getting pregnant. As the women reach by the age 40, these chances further fall down to 5% each month. The average age of menopause is 51, but according to a survey, most of the women become infertile before the arrival of menopause. But rare exceptions do exist and some females do get successfully pregnant in their mid-40s as well. These studies fall for natural fertility cycles as well as for fertility treatments like in vitro fertilization. Quality and quantity, both are affected by age (Bayrampour H and Heaman M, 2010).

Egg quality

Egg quality decreases with age, that's why women of advanced age are likely to have more miscarriages. The numbers of eggs are also likely to dwindle. These variations are most prominent in the late 30s therefore, is the most accurate parameter of testing egg quality (Joseph KS, et al., 2005).

Frequent genetic abnormalities known as aneuploidy are also observed in advanced age a female which also defines the quality of egg; in aneuploidy number of chromosomes fall or increase above the normal level. At the time of fertilization, there should be 23 chromosomes in a normal egg. This 23 number gets equalized by the 23 chromosomes coming from the sperm during fertilization giving birth to an embryo with normal 46 chromosomes. With age these numbers of chromosomes either become too high or too low, it means if fertilization takes place the baby will suffer. For instance, Down syndrome is such a case where embryo has an extra 21 chromosome. However, in many cases when the embryo has varied number of chromosomes it usually lead to miscarriages, and thus this reason elaborates why there are higher chances of miscarriages in women with advanced maternal age in comparison to young females.

Egg quantity

Loss of ovarian reserve occurs, which is the decrease quantity of egg containing follicles in the ovaries. Women gradually lose their ovarian reserve that leads to infertility and menopause. As all the follicles are present at the birth time of all the females, their loss began to occur with age because the pool might have been used up with time. As the ovarian reserves fall down, the sensitivity of follicles to the follicle stimulating hormone also decreases and they began to need more and more stimulation for an egg to get mature.

diminishing cycle is natural and age associated. However, if this issue occurs in women this might be due to smoking, ovarian surgery or some family history of early menopause.

Certain medical tests are available to detect the ovarian reserve, but they are not 100% efficient in predicting the pregnancy possibilities. These can detect age related changes but cannot tell when a female can conceive. Tests like hormone detection, i.e. oestrogen levels in blood during menstrual cycle are usually carried out. High oestrogen or FSH levels show low ovarian reserves. Moreover, ultrasound assessments and CCCT are also carried out for ovarian reserve detection. Undoubtedly, age has a lot to do with the obstetric characteristics of a female. In order to develop a comparative study of primiparous young and advanced maternal age women, the following work had been carried out to consolidate the stance.

METHOD

It was a cross sectional study and recruited the participants according to the inclusion criteria. Two groups were made in which 150 participants of primiparous women aged more than 35 years and 150 in other group of primiparous women aged 20 to 29 years. The low-income cut-off was determined for each respondent according to her family's total income, family size, and size of area of residence. Health-related information and behavior's consisted of 16 variables, including pre-pregnancy BMI, weight gain during pregnancy, knowledge of the benefits of taking folic acid before pregnancy, taking folic acid before pregnancy, smoking prior to pregnancy, feelings towards pregnancy, knowledge of pregnancy and labour and delivery (nine variables), and attendance at prenatal classes.

Variables studied in the obstetric characteristics category included a history of miscarriage, induced abortion, or use of fertility medications or medical procedures to become pregnant, and chronic medical conditions or health problems before pregnancy that required the woman to take medication for more than two weeks or have special care or extra tests during her pregnancy (Zasloff E, et al., 2007). Ninety-five percent confidence intervals were reported with each estimate. An alpha level of 0.05 was used for all statistical tests. Missing values were excluded from the analyses.

RESULTS

There was no statistically significant difference between the two groups in the proportion of women with a prepregnancy BMI in the overweight or obese category. Women of AMA were three times more likely to report having knowledge of the benefits of taking folic acid before pregnancy than younger women. Women of AMA were three times more likely to report having knowledge of the benefits of taking folic acid before pregnancy than younger women. The proportion of older women who took supplements containing folic acid in the three months

before pregnancy was 73%. Among younger women, this proportion was 51%. These women were less likely to have a family income below the low-income cut-off than women aged 20 to 29 years. The MES included a number of questions about whether women had enough information on topics related to pregnancy, labour, and birth (Fell DB, et al., 2005; Joseph KS, et al., 2003).

Women of AMA were significantly more likely than younger women to report having enough information about physical changes during pregnancy, emotional changes, warning signs of pregnancy complications, the process of labour and birth, what the husband or partner could do to support the mother during labour, pain management techniques during labour, the side effects of using pain medications and anesthesia during labour, and medical tests or techniques during pregnancy. Information about the effects of taking medication during pregnancy was the only option for which younger women were as informed as older women. It is noteworthy that 20% of younger women and 10% of older women reported that they were not informed about warning signs of pregnancy complications (PHAC, 2009).

Among women of AMA, 26.0% received most of their prenatal care from a family physician, 11.0% from a midwife, and 1.0% from other health care professionals. These percentages for women aged 20 to 29 were 37.7%, 4.9%, and 1.3%, respectively. Almost one quarter of women of AMA reported having a history of miscarriage, which was significantly more than younger women (Chalmers B, et al., 2008). There was no significant difference in reported history of induced abortion between the two groups. Older women were almost twice as likely as younger women to report having chronic medical conditions or health problems before pregnancy. Only 59.9% of older women gave birth vaginally, compared with almost three quarters of younger women. There were no significant differences in new born outcomes between the two groups.

DISCUSSION

The results of this secondary analysis confirm that women of AMA differ from younger women in several demographic and obstetric characteristics and in health behaviours and knowledge. Primiparous women of AMA were significantly more likely than younger women to have a high socioeconomic status. These results are consistent with the results of previous studies (Dzakpasu S, et al., 2008). Joseph et al. reported that the birth rate for nulliparous and multiparous women of AMA in Nova Scotia increased between 1988 and 2007, and this trend was more prevalent among nulliparous women with higher socioeconomic status. Poor medical and reproductive histories were significantly more prevalent among women aged ≥ 35 years.

Delbaere et al. found in a 2007 study that primiparous women aged ≥ 35 years were more likely than younger women to have become pregnant by means of assisted conception and to suffer from chronic complications during pregnancy such as hypertension and diabetes. Ziadeh and Yahaya reported in 2001 that, in comparison with women aged 20 to 29 years, women aged ≥ 35 years were at increased risk of higher weight gain, obesity, chronic and pregnancy-induced hypertension, antepartum haemorrhage, multiple gestation, mal-presentation, and premature rupture of membranes. Joseph et al. reported similar results regarding a history of infertility

and poor obstetric history among women of AMA. Advancing maternal age can be associated with declining fecundity, and older women are more likely than younger women to require infertility treatment to become pregnant. In addition, medical conditions and chronic diseases such as cardiovascular disease, arthritis, and diabetes are more prevalent among older women. The results of this study illustrated that women of AMA were more likely than younger women to engage in healthy behaviours before and during pregnancy. According to this review, the reasons for the increasing Caesarean section rate in women of AMA are not fully understood. The following factors might contribute to this phenomenon: an aging reproductive system, a lower clinical threshold for intervention among women of AMA, higher socioeconomic status, advancing age of the father, and medical-legal concerns. Interestingly, results of the current study illustrated women of AMA were more likely to be offered a Caesarean section or to request a Caesarean section before beginning labour. This finding suggests that women of AMA are more likely to consider a Caesarean section than younger women as are the providers of care for women of AMA. Joseph et al. stated that obstetric practice has adapted; that is, there have been reductions in midpelvic forceps use and increases in Caesarean section for breech presentation, labour induction, epidural anesthesia, and delivery by an obstetrician because of changes in maternal characteristics and concerns related to fetal and maternal safety. In previous reports, AMA has been identified as a determinant for several adverse pregnancy outcomes including LBW, SGA, and preterm birth.

While the increased risk of preterm birth and LBW in women of AMA are both very well documented, the association with SGA is more controversial.

Chan and Lao found no significant differences between younger and older women in rates of SGA, but Prysak et al. reported a difference at the 0.04 alpha level. In contrast to the findings of these previous studies, we found no significant differences in rates of preterm birth, LBW, or SGA between the two groups. However, there were trends to higher rates of preterm birth and LBW among women of AMA. It must be noted that in the MES survey, only women living with their infant at the time of the interview were included in the survey, meaning that women having a neonatal death due to preterm birth or LBW were excluded from the survey. The possibility exists that women of AMA may have been over-represented in the women who were excluded from the survey. There are several strengths associated with the MES. The MES used a large, randomly selected sample that is representative of the Canadian population. This survey provides a national perspective of maternity experiences among Canadian women. However, this survey has some limitations that should be considered in interpreting the results (PHAC, 2009).

CONCLUSION

Pregnant women of AMA are different from younger women in their characteristics and in some pregnancy outcomes. Population level studies provide useful information to identify modifiable factors in adverse outcome pathways. Women of AMA were advantaged in many aspects that might have a positive impact on pregnancy outcomes; they had generally higher socioeconomic status and were more likely to have planned pregnancies, to be informed about pregnancy, and to practice healthy behaviours than younger women. Conversely, women

of AMA were more likely to have chronic medical conditions or health problems before pregnancy than younger women. Women of AMA were at increased risk for some adverse pregnancy outcomes, mostly in the area of obstetrical interventions, such as higher rates of labour induction, Caesarean section, and assisted vaginal delivery. This raises a concern regarding increased obstetrical interventions for women of AMA. Whether this phenomenon is inevitable because of the effects of aging on the reproductive system, or whether it is mostly a result of labelling women of AMA as high risk should be explored in future studies. Older and younger women had similar preterm birth, SGA, and LBW pregnancy outcomes. This suggests that strategies to promote a healthy lifestyle and decrease modifiable risk factors are needed in the younger population of pregnant women.

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