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Adverse perinatal outcomes at advanced maternal age: An experience from a large Indian cohort

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Abstract
Background: The incidence of pregnancies at older age is on an increase internationally but there is disturbing body of evidence which implicates adverse perinatal outcomes in mothers at advanced age.
Patients and Methods: The study was conducted as an ambispective cohort study at a tertiary care Medical College Hospital over a period of 4and a half years from December 2013 to May 2018 to evaluate the outcomes associated with the risk.
Results: Obesity, higher socio-economic status, higher literacy and assisted conception appeared to be the statistically well associated with conception at advanced age. A statistically significant association was observed between the fetuses of older mothers developing foetal growth restriction (aRR-1.67, CI -1.37 – 1.98; P<0.001) and malpresentation (aRR-2.97, CI-2.43-3.55; P-<0.001). A significantly higher operative interference in terms of instrumental deliveries (P-0.003) and Caesarean section (P<0.001) was observed in mothers at advanced age. A 1.43 and 2.13 times higher risk of intrapartum foetal distress (P-0.002) and intrauterine death (<0.001) was also noted in these mothers. A significant difference in the birth weights was also noted with 2.86±0.81 kg vs 3.27±0.69 kg being noted in older and younger mothers respectively (P<0.001). Macrosomia and birth asphyxia did not have significant variation between the cohorts but APGAR scores at 1st and 5th minute varied significantly with neonates of older mothers at a 1.41 and 2.08 times higher risk of lower APGAR scores respectively. A relative risk of 1.82 (CI-1.38-2.37) in terms of perinatal mortality was observed in mothers with pregnancy at advanced age.
Conclusions: It is essential that women be in informed about the occurrence of such perinatal events at advanced age so that they can take informed decisions in best interest of the foetus and neonate.

Keywords: Adverse perinatal, advanced maternal, experience, Indian cohort

Introduction
The term advanced maternal age (AMA), first appeared in medical literature in 1950, to refer to pregnancies after 35 years of age [1]. The Royal College of Obstetricians and Gynaecologists (RCOG) has recognized a growing trend for child bearing to occur at AMA in Europe, Canada, Australia, New Zealand and the United States of America [2]. Though this fact is well established in the developing world, it has also been recognized in the developing world [3].
These changing patterns in childbearing can be attributed to social, educational and economic reforms towards gender equality, after feminist movement, which empowered women to participate in family planning and take decisions regarding their reproductive life [3-6]. Though these developments point towards a better gender development index, some authors from developing countries also attribute AMA to lack of family planning services, poverty, desire for a male child, cultural pre-disposition towards a large family size and exclusion of women from decision making [7]
AMA has been associated positively with adverse pregnancy outcomes (APO). There is increasing repository of evidence that makes it certain that women with AMA are at higher odds of antenatal complications like placental abruption, gestational diabetes mellitus (GDM), preterm labour (PTL) and pre-eclampsia in addition to adverse inta-partum outcomes like higher caesarean section rates, inceased chances of instrumental deliveries and post partum haemorrhage [5-9]. Studies have established that advanced maternal causes an imbalance between oxidative stress markers and angiogenic growth mediators which correlated well with adverse pregnancy outcomes. Increased serum soluble fms like tyrosine kinase 1 (sFlt1) and 8 epi prostaglandin F2 α (8 epi PGF2α) and decreased levels of placental growth factor (PlGF) and

total anti-oxidant capacity (TAC) have been demonstrated [10].

AMA independently and due to a wide spectrum of antenatal complications that it causes, places the foetus at higher risk for untoward events. Low birth weight (LBW), small for gestational age (SGA), neonatal acidosis, need for admission to Neonatal Intensive Care Unit (NICU), still births and neonatal deaths have been associated strongly with AMA [7-10]. These odds and relative risks appear to increase consecutively with increasing age [9, 10]. When pregnancies at extremes of age were compared neonatal complications like foetal distress, meconium aspiration, still birth, low Apgar scores and SGA were attributed exclusively to older mother [11]. As more irrefutable evidence accumulates over time, which establishes Barker's hypothesis, AMA and its related perinatal adversities can have huge ramifications in terms future populations having reduced physical and intellectual potential with a greater predisposition for development of disease conditions, which can be explained by foetal programming and this necessitates healthcare providers to provide necessary information to women at AMA or women planning for a conception at AMA.

This study was conducted with an aim to evaluate foetal and perinatal risk factors and outcomes in women at AMA. Secondary outcomes include socio-demographic and cultural factors which predispose to AMA.

Patients and Methods

The study was conducted as an ambispective cohort study at Employees State Insurance Corporation Medical College (ESICMC), Sanathnagar, Hyderabad, which is the largest ESIC tertiary care referral centre in the state catering to referrals from more than 35 ESIC hospitals and dispensaries in addition to its own patients. The data collected represents diverse; rural, semi-urban and urban populations of south India predominantly belonging to lower and middle income groups. The prospective component of the study included all maternities from December 2016 to May 2018 and the retrospective component included patients over three years from December 2013 to November 2016.

Over a four and a half year period we recorded a total of 16,289 maternities of which 13,076 entries were complete in all aspects. Retrospective data was collected from labour room (LR) registers and case sheets of patients were retrieved from medical records department (MRD). All data on antepartum status and, parturition and perinatal outcomes was recorded in a 4 section and 35 points data extraction sheet. AMA was defined as maternal age more than 35 years at the time of conception. Period of gestation was calculated for all purposes from scan findings in first trimester.

Antenatal cases aged > 35 completed years were considered as the study cohort and those between 21 and 35 years were considered as control cohort. Mothers who had not completed the 20th year were excluded from the study to avoid the bias of risk associated with teenage pregnancies and their APO. Similarly multi-foetal gestations were excluded to avoid the bias of their APO. Early pregnancy losses, miscarriages and medical terminations were not included in the parturition register. This bought the total cohort size to 11,785.

All variables were defined using standard operational definitions from RCOG and RCPCH guidelines. Clinical definitions were employed where quantitative definitions were not applicable. For macrosomia, Indian standards of > 4kg was used instead of international standards of >4.5kg. Differences were deemed statistically significant with p values < 0.05. Student's t test was used to analyse quantitative data and chi-square test was used to analyse qualitative data. Relative risk and relative risk adjusted to parity was calculated using SPSS, v23.

Results

A total of 926 mothers with age more than 35 years were noted which brings the incidence of the inclusion group to 7.85. Mean age in AMA group was 37.36±1.83yrs compared to 24.7±3.21yrs in control cohort. Socio-demographic factors which tend to be associated with AMA are higher socio-economic class, obesity, assisted conception, bad obstetric history (BOH) and higher literacy. There was a higher tendency at lower levels of care to refer cases with AMA to tertiary care centres. 41% of mothers with AMA were primigravidas. These have been presented in Table -1.

Table 1: Demographic and Obstetric Characteristics

S.No	Characteristic	Variables	AMA (> 35 yrs) n(%)	Maternal Age (21 – 35 yrs) n(%)	P (χ^2)	RR (95% CI)
1.	Total number (n)		926	10,859	-	-
2.	Percentage (of total births)		7.85	92.14	-	-
3.	Mean age (yrs) [M±SD]		37.36±1.83	24.7±3.21	S*	-
4.	Gravida	Primi	380(41.03)	3367(31.01)	S	Multiparity 0.85(0.80-0.90)
		Multi	546(58.96)	7492(68.99)		
5.	Socio economic status	Kuppuswamy 1& 2	347(37.47)	2498(23)	S	Kuppuswamy 4&5 0.70(0.64-0.76)
		Kuppuswamy 3	253(27.32)	2897(26.67)		
		Kuppuswamy 4 & 5	326(35.20)	5464(50.31)		
6.	Body Mass Index (BMI) in kg/m^2	Normal (18.5 – 24.9)	393(42.44)	6826(62.86)	S	Obese 1.55(1.46-1.65)
		Obese (> 25)	533(57.56)	4033(37.13)		
7.	Conception	Spontaneous	692(74.73)	10,063(92.66)	S	Assisted 5(4.5-5.7)
		Assisted	234(25.2)	796(7.33)		
8.	Booking visit	Registered	539(58.2)	8756(80.63)	S	Referral 2.5(1.99-2.35)
		Referred	387(41.79)	2103(19.36)		
9.	BOH	Absent	220(23.97)	2280(20.99)	NS	BOH 1.13(1.00-1.28)
		Present	706(76.24)	8579(79)		
10.	Education status	More than 12th class	481(51.94)	5104(47)	S	More literate 1.10(1.03-1.18)
		12th class or less	445(48.05)	5755(52.99)		

*- unpaired t test

Table 2 deals with direct risk factors the foetus is exposed to, during the antepartum period which can have adverse consequences before or after birth. Foetal growth restriction (FGR) also appeared to be 1.67 times more in mothers at AMA

when adjusted for parity, which appeared to e statistically significant. The occurrence of preterm labour (PTL) also appeared to be more in AMA group with a crude RR of 1.21 and adjusted RR of 1.05, but this association was not statistically very significant. Rupture of membranes after viability appeared to be higher in the AMA group but this was again statistically insignificant. Intrauterine death of the foetus after viability was significantly higher in older women with a 2.13 times higher chance compared to women aged 21 – 35 years.

Table 2: Foetal and perinatal risk factors in antepartum period in advanced maternal age versus normal maternal age

S.No.	Characteristic	AMA (> 35 yrs) (n=926)	Maternal Age (21 – 35 yrs) (n=10859)	P (χ^2)	RR (95% CI)	aRR (95% CI) adjusted for parity
1.	Fetal Growth Restriction(FGR)	136(14.6)	1010(9.3)	<0.001	1.58 (1.34-1.86)	1.67** (1.37 – 1.98)
2.	Preterm Labour (PTL)	168(18.14)	1628(15)	0.01	1.21 (1.05-1.40)	1.05 (0.73-1.34)
3.	Premature Rupture of Membranes (PROM)	85(9.17)	780(7.18)	0.02	1.28 (1.03-1.58)	1.07 (0.87-1.23)
4.	Malpresentation	127(13.71)	456(4.19)	<0.001	3.26 (2.71-3.93)	2.97** (2.43-3.55)

(** - association tested to be statistically significant)

The third section of the data extraction sheet dealt with risk factors which affect the foetus occurring during intrapartum period. The average gestational age at the onset of labour was significantly less in mothers with AMA at 36.92±1.91weeks compared to 38.79±1.35wks in control cohort. The chances of having a spontaneous vaginal delivery were relatively lower in elderly mothrs compared to their younger counterparts. Instrumental delivery and operative interference was significantly higher in AMA group which places their fetuses to have multiple adverse outcomes. Intrapartum foetal distress was significantly higher in the study cohort. These findings are tabulated below in Table 3.

Table 3: Foetal and perinatal risk factors during parturition in advanced maternal age versus normal maternal age

S.No.	Characteristic	AMA (> 35 yrs) (n=926)	Maternal Age (21 – 35 yrs) (n=10859)	P (χ^2)	RR (95% CI)	aRR (95% CI) adjusted for parity
1.	Mean Gestational Age at birth$^{\Delta}$ (weeks)	36.92±1.91	38.79±1.35	<0.001*	-	-
2.	Spontaneous vaginal Delivery (VD)	287(30.99)	4789(44.1)	<0.001	0.70 (0.64-0.77)	0.61** (0.51-0.69)
3.	Instrumental delivery (Forceps / Ventouse)	89(9.6)	760(6.99)	0.003	1.37 (1.11-1.69)	1.47** (1.27-1.77)
4.	Cesarean Section (CS)	550(59.39)	5310 (48.89)	< 0.001	1.21 (1.15-1.28)	1.54** (1.41-1.69)
5.	Intrapartum Foetal Distress $^{\Delta\Delta}$	109(12.48)	979(9.2)	0.002	1.35 (1.12-1.62)	1.43** (1.22-1.59)

Δ- Calculated over total live births | Δ Δ - calculated after removing IUFDs |
(*-students t test) | (** - association tested to be statistically significant)

Perinatal outcomes in control and study cohorts are illustrated in Table - 4. Low birth weight (LBW) was detected in 26.49% of babies at AMA compared to 15.05 in control cohort. This puts the babies of older mothers at 1.7 times higher risk of LBW. Macrosomia didn't vary significantly between the groups but with a lesser incidence in the neonates of AMA group. The total number of still births were 1.7 times higher in mother at AMA which was extremely significanr statistically. Birth asphyxia didn't appear to vary considerably between groups. The chances of having low APGAR scores at birth and 5 minutes were significantly lower in babies of mothers aged more than 35 years with an relative risk of 1.32 and 1.89 respectively, both of which are statistically significant. Apart from pre-existing mortality during gestation and parturition, an additional 1% of live births died during the first week of life compared to only 0.39% of such events in control cohort, which increases the risk of early neonatal loss by 2.6 times in older moters. Overall perinatal mortality appears to be significantly higher in mothers beyond 35 years with a relative risk of 1.82 at a percentage twice as much as younger mothers.

Table 4: Perinatal outcomes at advanced maternal age and normal maternal age

S.No.	Characteristic	AMA (> 35 yrs) (n=926)	Maternal Age (21 – 35 yrs) (n=10859)	P (χ^2)	RR (95% CI)	aRR (95% CI) adjusted for parity
1.	Intra Uterine Foetal Death (IUFD)	53(5.72)	283(2.6)	<0.001	2.20 (1.65-2.92)	2.13** (1.47-2.34)
2.	Intrapartum Foetal Deaths	16(1.72)	196(1.8)	0.86	0.96 (0.58-1.59)	0.91 (0.57-1.62)
3.	Live births	857(92.54)	10380(95.58)	<0.001	0.97 (0.95-0.99)	0.95** (0.91-1.02)
4.	Mean birth weight$^{\Delta}$ (kg) (live babies)	2.86±0.81	3.27±0.69	<0.001*	-	-
5.	Low Birth Weight $^{\Delta}$ (LBW)	227(26.49)	1562(15.04)	< 0.001	1.76 (1.56-1.98)	1.83** (1.62- 2.03)
6.	Macrosomia $^{\Delta}$	27(3.15)	446(4.29)	0.07	0.73 (0.50-1.07)	0.76 (0.32-1.29)

7.	Birth Asphyxia Δ	16(1.86)	219(2.11)	0.54	0.88 (0.53-1.46)	0.82 (0.41 – 1.82)
8.	APGAR - birth Δ (< 5)	69(8.05)	630(6.07)	0.03	1.32 (1.04-1.68)	1.41** (0.97-1.98)
9.	APGAR - 5 mins Δ (< 7)	51(5.95)	327(3.15)	<0.001	1.89 (1.42-2.52)	2.08** (1.22-2.89)
10.	Early Neonatal Death Δ	9(1.05)	41(0.39)	0.01	2.65 (1.29-5.45)	2.55** (0.91-4.29)
11.	Still births (IUFD + Intrapartum deaths)	69(7.45)	479(4.41)	<0.001	1.69 (1.32-2.15)	1.65** (1.01 – 2.4)
12.	Perinatal mortality (IUFD + Intrapartum deaths + early neonatal deaths)	78(8.4)	520(4.78)	<0.001	1.76 (1.40-2.21)	1.82** (1.38-2.37)

Δ – Calculated over total live births | (*-Students t test) | (** - association tested to be statistically significant)

Discussion

This study tries to assess the risk factors that AMA predisposes foetuses and neonates to, and also tries to evaluate the perinatal outcomes at AMA compared to pregnancies in younger women. Evidence based information in Indian population on the perinatal outcomes and risk factors of AMA are scarce. The existing data mainly comes from studies conducted on small cohorts. Our study recorded a 7.85% prevalence of pregnancy at AMA. This appears to vary significantly with multicentric studies in Turkey and Malaysia recording an incidence of 12.2% & 14.8% respectively whereas the Queensland Health statistics unit reported a 21% incidence [11 - 13].

There was a significant difference in the parity in both cohorts with primigravida mothers contributing 41% to the study cohort whereas only 31% to the control cohort, implying that in our population advanced maternal age is less common among multiparas (RR – 0.85), which could be attributed to a 5 times greater predisposition to have pregnancy at AMA after assisted conception. Ali Khatibi reported the occurrence of pregnancy after assisted techniques was more common in older pregnant women with almost 29% of all singleton pregnancies attributable to assisted conception [12]. Wu Y *et al* analysed and concluded in their study that among women who conceive with assisted techniques the risk of primary adverse outcomes like FGR and still birth is higher at very AMA compared to younger counterparts [13]. A lower socio economic status discourages pregnancies at AMA whereas higher educational status and food availability encourages it. Kebede *et al* analysed the role of low educational status and concluded that lower literacy in itself is a risk factor for adverse pregnancuy outcomes; further they elucidated that women with no education had an aRR of 2.15 and those with primary education had an aRR of 1.6, for adverse outcome in comparison to those with higher education [14]. Obesity and assisted conception are again linked by anovulatory subfertility and such association was illustrated by Karla *et al* [6]. Several such associations were then put forth by Louise for parity and obesity [9], Henry for obesity and education [15]. It can therefore be inferred that socio-economic and demographic characteristics have a complex interplay as risk factors to predispose women to conception at AMA.

It is now well established that there are several additional adverse outcomes observed in older pregnant women [3-9] that include but are not limited to gestational diabetes, gestational hypertension, overt diabetes, chronic hypertension and antepartum haemorrhage and it can be deduced that these could be attributed to indirectly increasing the risk of adverse foetal and neonatal outcomes. Similarly a number of other antepartum issues can directly affect the foetus like PROM, PTL, FGR and malpresentations. A recent meta analysis in the UK, established higher FGR at AMA which was attributed to placental dysfunction [16]. A 4.6 times higher risk of developing FGR was observed by Odame *et al* in women aged > 35 years [10], compared to a 1.65 times and 2.06 times higher risk described by Marie *et al* [11]. Such differences can be explained by the difference in proportion of various age strata in the studied subjects as mothers with AMA comprised half of the in Odame's study. We have also reported a significantly higher relative risk among older pregnant women which is in agreement with studies by Odame who mentioned significant increase in risk by 8.2 times [10], Ali Khatibi who described an increase by 14% [12] and Elizabeth who reported a 17.2% rise in preterm and 3.7% increase in very preterm deliveries at AMA [11]. The ageing process is said to cause uterine dysfunction which explains onset of preterm labour [11]. A systematic review derived a 1.96 times higher risk of preterm birth with an I^2 of 91% [17] in older women. PROM predisposes the foetus to infective morbidity and was found to be higher in elderly pregnant women and could be an explanation for higher preterm as PROM often causes spontaneous onset of labour.

Maternal age also appears to significantly modify several intrapatum characteristics to perinatal disadvantage. Operative interference in terms of vaginal and abdominal surgeries was found to be higher in the study participants. A 1.47 and 1.54 times additional relative risk was observed for instrumental vaginal delivery and caesarean section in older mothers. Similar findings echo from a study done by Elizabeth *et al* in Florida [18]. An age stratified study by Marie *et al*, describe aOR for vaginal delivery decreases with age with 0.43 at 35 – 39 years compared to 0.31 at > 40 years. Similarly, the odds for forceps and ventouse application increase with passing age with an aOR of 1.66 and 1.75; and 2.21 and 3.78 for forceps and ventouse respectively; at 35-39 yrs and > 40 years respectively [11]. Such instrumental deliveries become causes of several perinatal complications in the neonate. Intrapartum detection of foetal distress marks foetal hypoxia of varying levels and is a strong indicator of perinatal morbidity and this was also found to be 1.43 times higher at a significance level of P - 0.002 in our study. Marie *et al* have established a pattern wherein intrapartum foetal distress appears to increase with maternal age with aOR of 1.23, 1.51 and 1.6 in women aged 30-34, 3-39 and ≥40 years respectively [11].

Comparison of perinatal outcomes in both the groups, clearly demonstrates a bad prediction for babies of older mothers with a 1.83 times greater risk of low birth weight, similar concerns have been voiced by Odame and Goisis *et al* [10, 19]. The variation in the rates of birth asphyxia between both the groups appear to vary insignificantly but APGAR scores appear to have a distinct variation with lower scores among older women compared to younger women both at birth and 5 minutes after birth. A systematic review estimated a 2.49 times higher chance of lower scores in babies of older mothers, 5 minutes after birth [17]. Similarly Marie described the chances of lower APGAR at

AMA of ≥40 years is 1.51 times higher [11]. The incidence of macrosomia appeared to decrease with increasing age which could be explained by increase in growth restriction and low birth weight.

Intrauterine foetal demise was seen in order of 5.72% in elder mothers compared to 2.6% in younger mothers. Ali Khatibi *et al* have reported a 6% foetal demise after viability in mothers aged > 50 years in singleton pregnancies [12]. Still births appear to be significantly higher in fetuses of older mothers with our study evidencing a 1.65 times higher risk comparable with the findings of Wu Y, Marie and Lean *et al* who reported an heightened risk of 1.38, 1.75 and 2.34 respectively [13, 16, 11]. Early neonatal deaths were also increased with a risk ratio of 2.55, which is again in agreement with the findings of a recent meta analysis by Lean *et al* [16]. Table 5 compares the usual trends of perinatal outcomes at advanced ages in various studies.

Table 5: Comparative study of perinatal outcomes

S.No.	Study	Population	Age Stratification	LBW A(R)	Macro A(R)	Low APGAR (1) A(R)	Low APGAR (5) A(R)	Birth As. A(R)	Still birth A(R)	N. Death A(R)	Perinatal Mortality A(R)	Risk instrument
1.	Ogawa *et al* 2017 [4]	Japan	35 – 39 40 – 44 45 - 49	S(1.01) S(1.08) S(1.22)	-	-	S(1.05) S(1.12) S(1.11)	-	-	-	S(0.97) S(1.08) S(1.65)	Unadjusted RR
2.	Nelishan *et al* 2016 [20]	Turkey	-	1.6	1.5	-	-	-	1.1			Unadjusted OR
3.	Karla *et al* 2015 [6]	Brazil	-	1.83	1.22	1.58	1.49	1.38	-	-	-	Unadjusted OR
4.	Louise *et al* 2013 [9]	UK	30 – 34 35 – 39 >40	-	1.38 1.53 1.62	-	-	-	1.11 1.23 1.62	1.07 1.05 1.05	-	Unadjusted RR
5.	Rachael *et al* 2013 [21]	Australia	-		NS(0.96)					S(1.22)	S(1.32)	Unadjusted RR
6.	Mervan *et al* 2013 [22]	Turkey				NS	NS			S		Significance

A(R) – Association (A) by Chi square and Risk (R) in OR or RR, S – Statistically significant association, NS – statistically insignificant association
Macro – Macrosomia, Birth As. – Birth asphyxia, N Death – Neonatal death

Several mechanisms have been proposed to explain the pathophysiology of APO at AMA which include decrease in antioxidants with age which are supposed to fight free oxygen species and protect the foetus, several such antioxidant mechanisms have been found in placenta which decrease with age [23]. Another mechanism which has been put forth explains the occurrence of APO in relation to telomere length and telomerase activity (TA) which can be inferred because firstly, weak TA was noted in trophoblastic cells in IUGR foetuses [24]. Secondarily, hypoxia inducible factor-1α (HIF-1α) regulates placental growth and prevents free radical damage in pregnancy. It prevents hypoxic damage to foetus and HIF-1α has structural similarity to telomerase [25]. Lastly, maternal psychosocial stress and biological stress is supposed to reduce TA in mother [26] and TL has been found shorter in offspring's of mothers exposed to stress during pregnancy [27]. This by deductive logic means early cell death occurs in foetuses whose mothers have low TA.

Adding to the preexisting worrisome burden of perinatal adversities already known at AMA, what is the astonishingly disturbing is the increasing concern of the risk of developing malignancy in offspring born at AMA. One such recent finding of note is that by Imterat *et al* which establishes association between advanced maternal age and risk of development of childhood leukemia [28]. In wake of increasingly available evidence associated with such adverse outcomes it would not be an exaggeration to say that health education initiatives need to be taken to increase awareness about adverse perinatal possibilities if pregnancies are postponed.

Conclusions

Advanced age of the mother has profoundly undesirable and deleterious effects on the unborn and newly born. Needless to say, these adversities would interplay well into childhood and adulthood reducing intellectual, physical and emotional potentials. This does not imply that women should be advised to plan pregnancies at a younger age, putting their career plans at stake as this would prejudice and patronise their basic rights to live life at their terms, but rather it calls upon obstetricians to consider these pregnancies sensitively and empathetically and to provide women with options which they can utilize to make informed decision.

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