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Advanced maternal age and adverse maternal outcomes: Experience from a large Indian cohort

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Abstract
Introduction: It is very evident that pregnancies at advanced maternal age (AMA) is increasing internationally, due to multifactorial social socio-cultural and economic development. These pregnancies are associated with significant adverse pregnancy outcomes.
Patients & 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: Patients from higher socio-economic class, better education and more food availability appeared to have pregnancies at AMA. Such pregnancies place the patients at significant risk for development of hypertension (aRR – 1.53, 95%CI (1.22 – 1.60), P < 0.001) and diabetes (aRR – 1.23, 95%CI (1.36 – 1.94), P<0.001). The risk of antepartum haemorrhage and malpresentation also increases but premature rupture of membranes and preterm don't appear to be clearly associated. Older mothers are more likely to undergo a cesarean section with an aRR of 1.54 (95%CI, 1.15 – 1.28); P < 0.001 and less likely to have a vaginal delivery (aRR – 0.61; 95%CI, 0.51-0.69). Those having a vaginal birth are at higher risk of instrumental interference with an aRR of 1.47 (95%CI, 1.27-1.77). Post partum haemorrhage doesn't appear to significantly vary with a P value of 0.25. Intrapartum foetal distress also appears to be significantly higher (P-0.005) in older mothers (aRR – 1.43; 95%CI, 1.22-1.59).
Conclusions: AMA is associated with adverse maternal and fetal outcomes hence should be investigated to provide evidence based options to the patient which will aid in decision making.

Keywords: Advanced maternal age, antenatal complications, intrapartum outcomes

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 being recognized in the developing world as well [3].

These changing patterns in childbearing are attributed to social, educational and economic reforms towards gender equality that is empowering 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). Recent meta-analysis have shown women with AMA at higher odds of antenatal complications like placental abruption, gestational diabetes mellitus (GDM), preterm labour (PTL) and pre-eclampsia [8]. Several studies have elucidated higher odds of having adverse intra-partum characteristics in women at AMA in addition to antepartum and perinatal adversities [5, 7, 9]. These odds and relative risks appear to increase consecutively with increasing age [9, 10].

This study was conducted with an aim to evaluate pregnancy outcomes in women with AMA. Secondary outcomes included socio-demographic and cultural factors that predispose to AMA.

Patients and Methods

The study was conducted as an ambispective cohort study at tertiary Medical College Hospital in Hyderabad.

The data collected represents diverse; rural, semi-urban and urban populations of this part of the country 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 child births 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 3 section and 35 points data extraction form. 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 bias because of teenage pregnancies and their associated 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 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, 2017.

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 were 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 primigravida. These findings have been presented in Table-1.

Table 1: Comparison of demographic and obstetric characteristics: advanced maternal age versus normal maternal age

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 (Y) [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 Mas 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)		

Antenatal characteristics of both the groups have been summarized in Table 2 and the relative risk of each variable was calculated. Pregnancy induced hypertension (PIH) was significantly high with AMA (20.62% vs. 14.76%). The relative risk of having pre-eclampsia and eclampsia appeared higher in mothers >35 years (RR of 1.2 and 1.72 respectively), similarly the chances of chronic hypertension was 3.39 times higher at AMA. The spectrum of PIH also appeared to occur more significantly in mothers with advanced age even when adjusted for parity. Gestational and overt diabetes appear to be significantly associated with AMA as such and upon adjusting for confounding factor. Antepartum haemorrhage occurred more in AMA group with an RR of 1.8. Premature rupture of membranes (PROM) and preterm labour (PTL) also appeared more in AMA group but the association was not statistically very significant.

Table 2: Comparison of antepartum characteristics: 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.	Pregnancy Induced Hypertension (PIH)	191(20.62)	1603(14.76)	<0.001	1.40 (1.22–1.60)	1.53** (1.27-1.73)
1a.	Gestational HTN	37 (19.37 of 3.99)	577 (36 of 5.31)	<0.001	0.53 (0.40-0.72)	0.63** (0.51 – 0.79)
1b.	Pre-eclampsia	131	914	0.002	1.2	1.31**

		(68.58 of 4.14)	(57 of 8.41)		(1.08-1.34)	(1.05-1.41)
1c.	Eclampsia	23 (12 of 2.8)	112 (6.98 of 1.03)	0.12	1.72 (1.13-2.63)	1.47 (1.34 – 2.13)
2.	Chronic Hypertension	62(6.69)	214(1.97)	<0.001	3.39 (2.58-.47)	2.27** (1.87-2.66)
3.	Gestational Diabetes	121(13.06)	872(8.03)	<0.001	1.63 (1.36-1.94)	1.23** (0.92-1.44)
4.	Pre-gestational diabetes	156(16.84)	903(8.31)	<0.001	2.02 (1.73-2.37)	1.73** (1.21-2.27)
5.	Antepartum Haemorrhage	30(3.23)	195(1.79)	0.002	1.80 (1.23-2.63)	1.94** (1.33-2.71)
6.	Malpresentation	127(13.71)	456(4.19)	<0.001	3.26 (2.71-3.93)	2.97** (2.43-3.55)
7.	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)
8.	Preterm Labour (PTL)	168(18.14)	1628(15)	0.01	1.21 (1.05-1.40)	1.05 (0.73-1.34)

(** - association tested to be statistically significant)

The third section of the data extraction sheet dealt with intrapartum characteristics between the study and comparison cohorts and has been described in Table 3. The average gestational period was significantly less in mothers with AMA at 36.92±1.91 weeks compared to 38.79±1.35wks in control cohort. The chances of having a vaginal birth were only 2/3rd at AMA and still lesser when adjusted for parity. Instrumental deliveries and cesarean rates were significantly higher in AMA group irrespective of the parity. There is a higher probability of AMA mothers having an emergency section compared to an elective section with RR 0.94 and 1.12 respectively, but this doesn't appear statistically very strong and also becomes less distinctively differentiable upon adjusting for parity. There was an insignificant reduction in the occurrence of post partum haemorrhage. Perineal tears appear to reduce by 40% in mother >35 years. Intrapartum foetal distress diagnosed on electronic foetal monitoring was significantly higher in the study cohort. Deaths during parturition appeared to vary insignificantly between both the groups (p – 0.86). Total maternal deaths appeared to be more than double (RR – 2.60) in mothers with the risk factor.

Table 3: Comparison of Intrapartum characteristics: 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 (weeks)	36.92±1.91	38.79±1.35	<0.001*	-	-
2.	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	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)
4a.	Elective	352 (64 of 38.01)	3621 (68 of 33.3)	0.04	0.94 (0.88-1.00)	1.34** (1.13-1.43)
4b.	Emergency	198 (36 of 21.38)	1689 (31.8 of 15.55)	0.04	1.12 (1.00-1.27)	1.37** (1.19-1.41)
5.	Post Partum Haemorrhage (PPH)	135(14.5)	1737(16)	0.25	0.91 (0.77-1.07)	1.11 (0.89-0.1.34)
6.	Intrapartum Foetal Distress	109(11.77)	979(9.01)	0.005	1.30 (1.08-1.57)	1.43** (1.22-1.59)
7.	Intrapartum Foetal Deaths	16(1.72)	196(1.8)	0.86	0.96 (0.58-1.59)	0.91 (0.57-1.62)
8.	Perineal tears	21(2.26)	423(3.89)	0.01	0.58 (0.38-0.90)	0.99** (0.71-1.17)
9.	Total Maternal Deaths	4(0.43)	18(0.16)	0.08	2.60 (0.88-7.68)	2.41 (0.71-6.23)

(*-students t test) | (** - association tested to be statistically significant)

Discussion

The study tries to assess the effect of AMA on antepartum and intrapartum characteristics in Indian women. There is a dearth of evidence based information in Indian population with whatever available data arising from studies conducted on small cohorts. This scarcity of data implies that health care providers are less able to support women in their decision making process on evidence based norms. Our study recorded an occurrence of 7.85% of all pregnancies at AMA. A multicentric study in Turkey (2013) and Malaysia (2016) recorded an incidence of 12.2% & 14.8% respectively whereas the Queensland Health statistics unit recorded 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. Though there is increasing evidence that assisted conception in itself is a risk factor for adverse outcomes, Wu Y *et al* have clearly demonstrated in their study that women aged 35 – 42 years have a 1.29 times higher adjusted odds ratio of composite adverse outcomes including preeclampsia, abruption, foetal growth restriction and still birth compared to women aged 20 – 34 years, with both groups having conceived after assisted techniques [16]. A lower socio economic status discourages pregnancies at AMA whereas higher educational status and food availability encourages it. Similar associations have been described previously; obesity and assisted conception by Karla *et al* [6]; obesity and education by Henry *et al* [5]; Obesity by Saifon *et al* [12] and Parity and obesity by Louise *et al* [9].

Women at AMA appear to have significantly higher prevalence

of pre-existing hypertension and diabetes before embarking upon the pregnancy with an adjusted relative risk of 2.27 and 1.23 respectively. Similarly, the chance of development of hypertensive (1.53 times) and diabetic (1.23 times) states during pregnancy appears to be statistically higher in older women. These finding appear to be agreement with a recent meta analysis which found older mothers to have 2.85 and 1.99 times higher odds to develop diabetes and pregnancy induced hypertension during gestation [8]. Wu Y *et al* also reported a higher occurrence of preeclampsia in older pregnant women [16].

Antepartum haemorrhage also appears to be higher at advanced age with a 1.8 times higher risk to these mothers. Similar reports also come from Wu Y *et al* regarding placental abruption [16] and Roustaei Z *et al* who exclusively studied women with placenta previa and evaluated the odds of maternal adverse outcomes in older and younger women wherein older women with previa were found to have an odds ratio of 7.3 compared to 6.8 in younger women [17]. Though PROM and PTL appear be higher in the study cohort the association doesn't appear statistically significant with P values of 0.02 and 0.01 respectively. A large study conducted by Goisis A *et al* on 124,098 maternities safely concluded that the total increase in the risk of preterm birth was 1% and 2% in women aged 35 to 39 years and ≥40 years; respectively, thereby describing the finding as statistically and substantively insignificant [18] reported a 2% increase in the risk of preterm. On the other hand malpresentations appear to occur in 13.7% of older mother compared to 4.19% of younger counterparts, which put these mothers at a 2.97 times higher risk. Another large meta analysis of 7 studies reveals a relative risk of 1.45 for the occurrence of preterm labour in mothers older than 35 years [8].

Intrapartum characteristics also varied significantly between the groups in terms of lesser incidence of vaginal birth (30.99% vs. 44.1%) and perineal tears (2.26% vs. 3.89%) in the study cohort. Instrumental deliveries and cesarean sections occurred more in older mothers with a 1.47 and 1.54 times higher risk respectively. Elective cesarean section was observed more in younger mother's cohort whereas emergency section happened more in mothers with AMA which can be explained due to higher occurrence of pregnancy complications. A study by Odame *et al* observed an aOR of 2.17 and 2.7 for emergency and elective caesarean section [19]. During labour, foetal distress patterns on cardiotocography were predominantly seen in the study group with an aRR of 1.43. 1.72% of all the maternities in the AMA group ended in intrapartum foetal distress compared to 1.8% in women aged 21 – 35 years which was found to be statistically insignificant. Overall AMA placed women at a higher risk of intrapartum complications especially in terms of operative interference and instrumental deliveries. This could be attributed to the multiple antenatal complications that are significantly increased in this group. A recent study by Kahveci *et al* reaffirms the fact that the need for operative interference is high in older women [20]. This fact is also reiterated in several studies by Henry [5], Jean [7], Rachael [13] and Azar [15]. A significantly high maternal mortality was seen in mothers > 35 years putting them at a 2.6 times higher risk than their counterparts. Few of the antepartum and intrapartum outcomes from studies with similar research methodologies have been compared in Table 4.

Table 4: Comparison of maternal outcomes with advanced maternal age

S. No.	Study (Country)	PIH A(R)	GDM A(R)	APH A(R)	MP A(R)	FGR A(R)	PTL A(R)	VD A(R)	CS A(R)	Ins A(R)	PPH A(R)	F.Dis A(R)	Reference
1.	Maryam *et al* (Iran)	S	S	NS	-	NS	NS	S	S	-	-	-	[3] 2015
2.	Henry *et al* (Malaysia)	S (6.61)*	S (3.11)*	-	-	-	NS	S	S (1.76)*	S (1.09)*	-	-	[5] 2016
3.	Jean *et al* (Africa)	S (4)	-	S (2.25)	NS	NS	S (1.3)	S (0.86)	S (1.76)	NS	S (2)	S (2.69)	[7] 2013
4	Khalil *et al* (British)	S (1.01)*	S (1.06)*	-	-	S (0.98)*	-	S	S (1.09)*	-	-	-	[10] 2013
5	Saifon *et al* (Thailand)	S	S	NS	-	-	S	S	S	S	-	-	[12] 2013
6	Rachael *et al* (Australia)	S (1.03)	S (1.87)	NS (1.06)	-	-	S (1.11)	-	S (1.41)	S (0.92)	S (0.88)	S (0.85)	[13] 2013
7	Amarin *et al* (Jordan)	S	S	S	-	-	NS	S	S	NS	NS	-	[14] 2013
8	Azar *et al* (Iran)	S (2.21)*	S (1.27)*	NS (0.81)*	NS (0.53)*	-	S (1.29)*	-	S (3.77)*	-	-	-	[15] 2011

A(R) – Association (A) by Chi square and Risk (R) in OR or RR, S – Statistically significant association, NS – statistically insignificant association, () Relative Risk, ()* Odds Ratio

MP – Malpresentation, Ins – Instrumental, F Dis – Foetal Distress, Per. T – Perineal Tears

The most prominent confounding factor for the study was the parity as it independently effects various obstetric outcomes, hence adjusted odds ratios were evaluated accordingly. Most of the associations remain statistically valid even after univariate logistic regression. This fact is further strengthened by studies by Kahveci [20] and Kebede *et al* [21]. Kahveci *et al* studied adverse outcomes in nulliparous singleton pregnancies with respect to age and concluded that the development of gestational diabetes and hypertension and caesarean section rates are higher in elderly primigravida mothers [20]. Further fortification can be derived from the study design used by Kebede wherein mothers were stratified based on increasing age and the dynamics observed in odds ratio clearly demonstrated that increasing age can continually increase the risk of adversities. There is no cut off age before which pregnancy can be considered safe and similarly nothing numerical beyond which patient can be counseled for avoidance of pregnancy. The study noted a 2.54 times higher risk of adverse outcomes in age group 35 – 44 years, 2.79 times higher risk in 45 – 54 years group and 4.18 times in women > 55 years considering women < 24 years as comparison group [21].

An considerable scientific explanation for the occurrence of

these adverse affects comes from a fact that oxidative stress increases and antioxidant capacity decreases with advancing age. A study conducted by Odame *et al*. brings this to certainty, wherein mothers with advanced maternal age were found to have an imbalance between oxidative stress markers and angiogenic growth mediators which correlated well with adverse pregnancy outcomes. Noteworthy findings of the study included 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). A negative correlation was observed between AMA and PlGF:sFlt1 ratio and with a r value of -0.475 and a positive correlation between AMA and 8 epi PGF2α: PlGF ratio [19]. Considering such eventualities it would not be an exaggeration to echo the views of Sauer *et al*, in his paper where the author urges obstetricians to illuminate patients with pragmatic and evidence based knowledge about the possibility of compromised outcomes of having a pregnancy at advanced age [22].

Conclusions

Advanced age of the mother has profoundly undesirable and deleterious effects on the pregnancy during antenatal period, during delivery and in the immediate post partum phase. This does not imply that women should put their career at stake to plan an early pregnancy but rather elucidates the fact that women need to be well informed by health care providers to empower them to take an informed decision.

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