The risk of birth defects is not associated with semen parameters or mode of conception in offspring of men visiting a reproductive health clinic

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Submitted on June 19, 2018; resubmitted on January 1, 2019

STUDY QUESTION: What is the relationship between semen parameters and birth defect (BD) rates in offspring of men evaluated for infertility?

SUMMARY ANSWER: Among men undergoing infertility evaluation, there is no significant relationship between semen parameters and defect rates in live or still births, even when considering mode of conception.

WHAT IS KNOWN ALREADY: Approximately 15% of couples have fertility difficulties, with up to a 50% male factor contribution. An increased risk of BDs exists in couples using ART, particularly IVF and ICSI, but it is unknown if this related to the ART procedures or an underlying male factor.

STUDY DESIGN, SIZE, DURATION: To determine if the severity of male factor infertility, as assessed via sperm quality and mode of conception, is associated with BD rates, we performed a retrospective cohort study. Fathers with semen analysis data in the Baylor College of Medicine Semen Database (BCMSD) were linked with their offspring using Texas Birth Defects Registry (TBDFR) data between 1999 and 2009. In this 10-year period, a total of 1382 men were identified in linkage between the BCMSD and TBDFR. A total of 109 infants with and 2115 infants without BDs were identified.

PARTICIPANTS/MATERIALS, SETTING, METHODS: To determine the association between BDs and semen parameters, we used hierarchical linear modeling to determine odds ratios between BD rates, semen parameters, and mode of conception before and after adjustment for paternal, maternal and birth covariates. Semen parameters were stratified based on thresholds defined by the WHO fifth edition laboratory manual for the examination and processing of human semen.

MAIN RESULTS AND THE ROLE OF CHANCE: In total 4.9% of 2224 infants were identified with a BD. No statistically significant association was observed between BD rates and semen parameters, before or after adjustment for covariates. The association between sperm concentration and BDs demonstrated an odds ratio (OR) of 1.07 (95% confidence interval: 0.63–1.83); motility: OR 0.91 (0.52–2.22); and total motile count: OR 1.21 (0.70–2.08). Likewise, mode of conception, including infertility treatment and ART, did not affect BD rates ($P > 0.05$).

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LIMITATIONS, REASONS FOR CAUTION: BDs recorded in the TBDFR only include live born infants or still births after 20 weeks, our study did not evaluate the effect of impaired semen parameters on developmental defects prior to 20 weeks of gestation. With 109 BDs, our statistical analysis was powered to detect moderate differences associated with particular semen parameters. Additionally, data about mode of conception was not available for 1053 of 2224 births.

WIDER IMPLICATIONS OF THE FINDINGS: BD rates are not associated with semen quality or mode of conception. The current study suggests that the severity of male factor infertility does not impact the rate of congenital anomalies. This information is important when counseling couples concerned about the relationship between impaired semen quality and BDs.

STUDY FUNDING/COMPETING INTEREST(S): Supported in part by the NIH Men's Reproductive Health Research (MRHR) K12 HD073917 (D.J.L.), the Multidisciplinary K12 Urologic Research (KUR) Career Development Program (D.J.L.), P01HD36289 from the Eunice Kennedy Shriver National Institute for Child Health and Human Development, NIH (D.J.L.), and by U01DD000494 from the Centers for Disease Control and Prevention and the Title V Block Grant to the Texas Department of State Health Services. A.W.P. is a National Institutes of Health K08 Scholar supported by a Mentored Career Development Award (K08DK115835-01) from the National Institute of Diabetes and Digestive and Kidney Diseases. This work is also supported in part through a Urology Care Foundation Rising Stars in Urology Award (to A.W.P.) None of the authors has a conflict of interest.

TRIAL REGISTRATION NUMBER: Not applicable.

Key words: male infertility / semen / sperm count / sperm motility / congenital abnormalities

Introduction

The World Health Organization estimates that worldwide, 48.5 million (15%) couples are infertile (Mascarenhas et al., 2012). A male factor is solely responsible for infertility in 40% of these couples and contributory in another 20% (Thonneau et al., 1991; Chandra et al., 2005; Hwang et al., 2011). Evaluation of the infertile male includes a history, physical exam, hormone evaluation and semen analysis. Semen parameters classify men into abnormal subfertile and normal fertile categories. The diagnosis of infertility can be made only in the absence of sperm in the ejaculate, making the semen analysis a crude indicator of fertility potential (Guzick et al., 2001). Despite this diagnostic approach, a distinct cause for infertility is not identifiable in up to 50% of infertile males. Many of these idiopathic infertility cases are likely genetic or genomic in nature (Dohle et al., 2005; Hwang et al., 2010).

In the era of ART, IVF and ICSI have revolutionized conception in infertile couples. However, ART is not without risks, which include transmission of genetic or genomic disease to the offspring and a 30–40% increased risk of birth defects (BD) in the children (Hansen et al., 2005; Davies et al., 2012; Wen et al., 2012). Furthermore, a longitudinal study by Zhu et al. (2006) demonstrated an increased risk of BD associated with infertility, even when accounting for ART use.

While impaired semen parameters have been independently associated with various pathologic conditions and a higher mortality risk in the man, the relationship between semen parameters and BDs of the offspring has been incompletely defined (Eisenberg et al., 2013a, 2014, 2015a, 2015b). In this study, we sought to determine the relationship between a father's semen parameters and BD of the child in a contemporary cohort of men evaluated for infertility.

Materials and Methods

After Institutional Review Board approval from Baylor College of Medicine and the Texas Department of State Health Services, a retrospective chart review was performed to identify men who had undergone a fertility evaluation at the Baylor College of Medicine and had at least one complete

semen analysis between 1999 and 2009 in the Baylor College of Medicine Semen Database (BCMSD). Men were included if they met the following inclusion criteria: (i) were of reproductive age, defined as 20–50 years old, (ii) presented for fertility evaluation and (iii) had semen analysis data. For men with multiple semen analyses, results of the first semen analysis were analyzed. Men were excluded if they had a history of vasectomy and post-vasectomy semen analyses. Electronic medical records were reviewed to obtain demographic information for both the father and mother of the offspring.

Fathers with semen analysis data in the BCMSD were linked based on name and date of birth with offspring in the Texas Birth Defects Registry (TBDFR) using data from 1999 to 2009. Data from these years were included in this analysis.

Data on total live births came from Texas birth certificate data; such a certificate is required by law for every birth in the state showing signs of life. Fetal death data were taken from fetal death certificates, which are required for any Texas pregnancy over 20 weeks gestation that does not result in a live birth. Both live and fetal death certificate datasets were provided by the Center for Health Statistics at the Texas Department of State Health Services (DSHS). Certificate data were also used as a source for all father and mother sociodemographic characteristics (age, race/ethnicity, education, birthplace), and pregnancy characteristics (plurality, preterm birth, year of delivery).

The TBDFR data were analyzed to identify offspring with and without BDs and to collect information regarding the nature of the BD. The TBDFR is an active surveillance system of infants and fetuses with structural or chromosomal BDs born to mothers residing in Texas at the time of delivery. TBDFR staff review medical records in hospitals, birthing centers and midwifery locations, and enter relevant information for cases into a web-based system where it undergoes extensive quality checks. All diagnoses were made prenatally or within 1 year after delivery. The TBDFR includes all pregnancy outcomes regardless of gestational age: live births (96.6% of cases), spontaneous fetal deaths (1.8%) and pregnancy terminations (1.5%).

Statistical analysis

Using the child as the unit of analysis, father, mother and pregnancy characteristics were analyzed to see if there was any association with BD status

(yes/no) and with semen sample characteristics; this used a chi-square test or a Fisher's Exact Test where cell sizes were too small (Table I).

For analyzing the association between father's semen sample characteristics and BDs in offspring, a case-control approach was used; children with any BD were considered cases and children without a BD controls. Semen parameters were stratified based on subfertile cutoffs defined by the WHO fifth edition laboratory manual for the examination and processing of human semen (World Health Organization, 2010). The unit of analysis was the child, and logistic regression provided the OR and its 95% confidence limits (95% CI). Because 842 of 2224 (37.9%) children were siblings of the same father, data points could not be considered independent. Thus the logistic regression incorporated multi-level modeling, with children as the first level and fathers as the level above that, using PROC GLIMMIX in SAS (Cary, NC, USA). That was done both for crude (Table II) and adjusted analyses (Table III). All available covariates were adjusted for in order to minimize potential alternate explanations for the association of semen parameters with BDs. With our sample size and ratio of cases to controls, we had 80% power to detect an odds ratio of 1.7 with $P < 0.05$. However, because father and mother covariates tend to be highly correlated (e.g. older fathers tend to live with older mothers), additional models were run with the father and mother covariates separated.

Results

Between the years of 1999 and 2009, 1382 men underwent both a semen analysis as part of their fertility work-up at BCM and had offspring (Supplementary Table S1). Demographic data were available for both the father and the mother associated with all the samples screened. The majority of the fathers and mothers were between the ages of 20 and 29 (63.3 and 72.3%, respectively); 21.4% of the fathers and 19.1% of the mothers were <20 , and 15.3% of the fathers and 8.6% of the mothers were over 29. The predominant race/ethnicity and education level for both the fathers and mothers screened were Caucasian and greater than a high school level diploma (Table I).

Of the 2224 offspring found, 109 (4.9%) children had 229 BDs according to data in the Texas BDs Registry. The three most frequent BDs, in decreasing order, were ostium secundum type atrial septal defect (26), obstructive defects of the renal pelvis or ureter (14), and ventricular septal defects (13). By organ system, cardiovascular ($n = 77$) and musculoskeletal ($n = 60$) defects were the most common, 48 genitourinary defects were detected (Supplementary Table SII).

When the parents of the affected offspring were compared to the parents of the non-affected offspring, no significant difference was seen between the age, race/ethnicity, country of origin or education level of either parent (Table I). However, parents of offspring with BDs were more likely to have plural pregnancies (twins, triplets, etc.), deliver prematurely ($P < 0.0001$) and to give birth in later years.

No significant association was observed between BDs and semen analysis parameters, including sperm concentration, motility, semen volume, total sperm count, and total motile sperm count (Table II) both when considering semen parameters as a continuous variable ($P > 0.05$) and when categorizing semen parameters as above or below the lower limits of normal defined by the WHO fifth edition laboratory manual for the examination and processing of human semen. This lack of association persisted after adjusting for paternal and maternal covariates (Table III).

Discussion

BD are present in 1 of every 33 births and are the leading cause of infant mortality worldwide (Centers for Disease Control and Prevention, 2008). The majority of anatomic anomalies are non-syndromic, affect a single organ system, and result from interactions between the genetics and environmental exposures *in utero* (Ailes et al., 2014; Hobbs et al., 2014). Epidemiologic studies have identified several environmental factors predisposing to BD including *in utero* exposure to toxins, such as tobacco, alcohol and medications. With advances in genetic technologies, however, genetic and epigenetic factors are increasingly being identified.

While semen parameters alone are overall poor predictors of fertility status, worse semen parameters are associated with higher rates of genetic and genomic anomalies, including structural chromosomal abnormalities, mutations and aberrant epigenetic regulatory mechanisms (Matzuk and Lamb, 2008). Similarly, important associations have also been made between suboptimal semen parameters and paternal risk of morbidity, malignancy and mortality (Raman et al., 2005; Eisenberg et al., 2013b, 2015a, 2015b). In a cross-sectional study by Eisenberg et al. (2015a), men with low ejaculate volume, reduced sperm motility, and poor morphology were more likely to have higher Charlson Comorbidity Index scores. In a subsequent study, Eisenberg et al. (2014) linked oligozoospermia and poor motility with a higher mortality rate. Two additional studies associated reduced sperm concentration, impaired sperm motility and abnormal sperm morphology with an increased risk of testicular cancer (Jacobsen et al., 2000; Raman et al., 2005). These studies underscore that impaired semen parameters are associated with poor male health.

In this study, we compared conventional semen parameters with the occurrence of non-syndromic BDs in offspring and found no association between any semen parameters and the presence of BD, despite adjustment for paternal and maternal covariates. The observed narrow 95% confidence intervals in our results supports a large enough cohort size, indicating that findings were not missed due to a lack of statistical power. Indeed, we were able to identify known risk factors for BDs; full-term singletons were highly significantly less likely to have BD compared to preterm infants and infants born with a higher birth plurality. Regardless of the confidence interval size, the odds ratio point estimates were all close to the null (1.00), further suggesting that no underlying association with semen parameters exists in our study. Among the BDs assessed, we observed a higher rate of cardiac and renal malformations, which reflects the general experience in the TBDFR.

Studies comparing male factor infertility with BD are few, of limited sample size, and lack agreement in their findings. Fedder et al. compared 466 children conceived using testicular or epididymal sperm extraction and ICSI to children conceived using ICSI with ejaculated sperm, children conceived using IVF and children born after natural conception as controls (Fedder et al., 2013). The authors linked the Danish IVF Register, Medical Birth Register and National Hospital Discharge Register and found a 7.7% overall BD rate among children born following surgical sperm extraction and ICSI, which did not significantly differ with the other three control groups. Significant differences were present within specific organ systems, including a higher rate of bone or cartilage neoplasms among twin children conceived following surgical sperm extraction and ICSI, compared to ICSI performed using

Table 1 Description of covariates overall and by birth defect status among children in the cohort, Texas 1999–2009.

Characteristic	Whole cohort		With birth defects		Without birth defects		P value*
	n	(%)	n	(%)	n	(%)	
Total	2224	(100.0)	109	(100.0)	2115	(100.0)	
Father's age							
<30	476	(21.4)	18	(16.5)	458	(21.7)	0.40
30–39	1408	(63.3)	75	(68.8)	1333	(63.0)	
40+	340	(15.3)	16	(14.7)	324	(15.3)	
Missing	0		0		0		
Father's race/ethnicity							
White non-Hispanic	1540	(69.7)	79	(73.2)	1461	(69.5)	0.82
Black non-Hispanic	171	(7.7)	7	(6.5)	164	(7.8)	
Hispanic	299	(13.5)	12	(11.1)	287	(13.7)	
Other non-Hispanic	201	(9.1)	10	(9.3)	191	(9.1)	
Missing	13		1		12		
Father's education							
<High school	73	(3.3)	5	(4.6)	68	(3.3)	0.12
High school	197	(9.0)	4	(3.7)	193	(9.3)	
>High school	1923	(87.7)	99	(91.7)	1824	(87.5)	
Missing	31		1		30		
Mother's age							
<30	425	(19.1)	14	(12.8)	411	(19.4)	0.08
30–39	1608	(72.3)	89	(81.7)	1519	(71.8)	
40+	191	(8.6)	6	(5.5)	185	(8.8)	
Missing	0		0		0		
Mother's race/ethnicity							
White non-Hispanic	1449	(65.2)	70	(64.2)	1379	(65.3)	0.97
Black non-Hispanic	154	(6.9)	7	(6.4)	147	(7.0)	
Hispanic	381	(17.2)	19	(17.4)	362	(17.1)	
Other non-Hispanic	237	(10.7)	13	(11.9)	224	(10.6)	
Missing	3		0		3		
Mother's education							
<High school	76	(3.4)	4	(3.7)	72	(3.4)	0.83
High school	220	(10.0)	9	(8.3)	211	(10.1)	
>High school	1912	(86.6)	96	(88.1)	1816	(86.5)	
Missing	16		0		16		
Plurality							
Singleton birth	1646	(74.0)	57	(52.3)	1589	(75.1)	<0.0001
Twins, triplets, etc.	578	(26.0)	52	(47.7)	526	(24.9)	
Missing			0		0		
Preterm birth							
Yes	518	(23.4)	47	(43.1)	471	(22.3)	<0.0001
No	1700	(76.7)	62	(56.9)	1638	(77.7)	
Missing	6		0		6		
Year of infant birth							
1999–2005	1049	(47.2)	40	(36.7)	1009	(47.7)	0.02
2005–2009	1175	(52.8)	69	(63.3)	1106	(52.3)	
Missing			0		0		

Continued

Table I *Continued*

Characteristic	Whole cohort		With birth defects		Without birth defects		P value*
	n	(%)	n	(%)	n	(%)	
Pregnancy resulted from infertility treatment**							
Yes	258	(22.0)	21	(30.4)	237	(21.5)	0.08
No	913	(78.0)	48	(69.6)	865	(78.5)	
Missing	1053		40		1013		
Pregnancy resulted from fertility-enhancing drugs, artificial insemination, intrauterine** insemination							
Yes	191	(16.3)	16	(23.2)	175	(15.9)	0.11
No	980	(83.7)	53	(76.8)	927	(84.1)	
Missing	1053		40		1013		
Pregnancy resulted from assisted reproductive technology**							
Yes	63	(5.4)	4	(5.8)	59	(5.4)	0.87
No	1108	(94.7)	65	(94.2)	1043	(94.7)	
Missing	1053		40		1013		

*P value for no difference in distribution of characteristic between children with and without birth defects. Does not include missing category.

**As determined from data reported in the birth certificate or fetal death certificate.

Table II Association of semen parameters with birth defects in offspring, Texas 1999–2009, additionally requiring that men have testicular failure and using hierarchical modeling.^a

	With birth defects		Without birth defects		Crude odds ratio	
	n ^b	(%)	n ^b	(%)	Estimate	(95% CI) ^c
All Infants	109	(100.0)	2115	(100.0)		
Concentration ^d						
<15	47	(43.1)	900	(42.6)	1.02	(0.68–1.52)
≥15	62	(56.9)	1215	(57.5)		
Motility ^d						
<40	41	(37.6)	761	(36.0)	1.07	(0.71–1.61)
≥40	68	(62.4)	1354	(64.0)		
Volume ^d						
<1.5	18	(16.5)	375	(17.7)	0.92	(0.54–1.57)
≥1.5	91	(83.5)	1740	(82.3)		
Total sperm count ^d						
<39	49	(45.0)	989	(46.8)	0.93	(0.62–1.38)
≥39	60	(55.1)	1126	(53.2)		
Total motile count ^d						
<9	43	(39.5)	789	(37.3)	1.09	(0.73–1.64)
≥9	66	(60.6)	1326	(62.7)		

^aIn men with testicular failure and using hierarchical modeling.

^bMay not add up due to missing values.

^c95% confidence interval.

^dSemen parameter cut points as defined by lower limit of normal in the WHO fifth edition laboratory manual for the examination and processing of human semen.

ejaculated sperm (0.03) and natural conception ($P = 0.04$). Additionally, singleton boys conceived using sperm extraction and ICSI had higher rates of cardiac malformations, including Tetralogy of Fallot and ventral septal defects, compared to singleton boys conceived using conventional IVF or natural conception. No differences were observed

between children conceived using ICSI with surgically extracted sperm or ejaculated sperm, suggesting ICSI as a possible culprit for the higher BD rate. The results of this study corroborate the present study's findings of a higher rate of cardiac malformations, although no significant difference between groups was observed. Esteves and Agarwal

Table III Adjusted association of semen parameters with birth defects in offspring, Texas 1999–2009, additionally requiring that men have testicular failure and using hierarchical modeling. Includes adjustment for using type of infertility treatment (drugs etc., assisted reproductive technology, none).

Characteristic	Categories examined	Odds ratio, adjusted for all covariates ^a		Odds ratio, adjusted for father covariates ^b		Odds ratio, adjusted for mother covariates ^c	
		Estimate	(95% CI) ^d	Estimate	(95% CI)	Estimate	(95% CI)
Concentration	< 15 ≥ 15	1.07	(0.63–1.83)	1.08	(0.64–1.82)	0.99	(0.59–1.68)
Motility	< 40 ≥ 40	0.91	(0.52–1.59)	0.90	(0.52–1.55)	0.82	(0.47–1.41)
Volume	< 1.5 ≥ 1.5	1.08	(0.52–2.22)	1.10	(0.54–2.24)	1.05	(0.52–2.13)
Total sperm count	< 39 ≥ 39	0.89	(0.51–1.53)	0.89	(0.53–1.51)	0.84	(0.49–1.41)
Total motile count	< 9 ≥ 9	1.21	(0.70–2.08)	1.18	(0.69–2.01)	1.09	(0.64–1.85)

^aFather's age, birthplace, education, race/ethnicity; mother's age, birthplace, education, race/ethnicity; infant's birth year, plurality of the pregnancy, type of infertility treatment.

^bFather's age, birthplace, education, race/ethnicity; infant's birth year, plurality of the pregnancy, type of infertility treatment.

^cMother's age, birthplace, education, race/ethnicity; infant's birth year, plurality of the pregnancy, type of infertility treatment.

^d95% confidence interval.

retrospectively analyzed data from 370 azoospermic men who underwent 471 ICSI cycles using surgically extracted sperm compared with 621 ICSI cycles using ejaculated sperm, with an overall BD rate of 1.6% which did not differ between groups (Esteves and Agarwal, 2013).

Several studies have examined the rate of BD with IVF and/or ICSI (Wen et al., 2012). Births after ART were associated with an increased risk of BD in an observational study by Davies et al., who compared the BD risk among 6163 births using ART to 302,811 spontaneously conceived births (Davies et al., 2012). After controlling for the mode of conception, IVF use was not associated with a significantly increased risk of BD (multivariate OR 1.1 [95% CI 0.9–1.3]); however, the increased risk associated with ICSI remained (multivariate OR 1.6 [95% CI: 1.3–1.9]). Recently, Seggers et al. (2015) examined the association between IVF/ICSI and BD among Norwegian children with BD and found an increased risk of abdominal wall defects with parental subfertility (OR 2.43, 95% CI: 1.1–5.6), followed by penoscrotal hypospadias (OR 9.8, 95% CI: 3.6–27.0) and right ventricular outflow tract obstruction (adjusted OR 1.7, 95% CI: 1.1–3.0). However, the authors did not categorize subfertile couples based on male or female factor fertility or by sperm characteristics. The present study suggested a trend toward a higher rate of BDs in children conceived with ART.

Several limitations exist in the current study, primarily related to its retrospective design, including a possible underestimate of the effect of male factor infertility, as our population represented all semen data obtained from all men who underwent fertility evaluation. Only the first semen analysis was included in this analysis and strict morphology was also not assessed among the semen parameters, limiting our evaluation. While multiple semen analyses from each male partner is better for stratifying men by WHO guideline semen parameters (Chiu et al., 2017), we demonstrate that semen parameters are not significantly associated with BDs when assessed as a continuous variable nor when dichotomized with WHO manual reference values. Furthermore, while men in our study underwent routine genetic evaluation with karyotype, Y chromosome microdeletion and cystic fibrosis screening, no comparisons were made between the subgroup of men with identified genetic abnormalities and BD in their offspring. Our study did not control for maternal factors including

age, folic acid intake and other environmental exposure such as certain medications, all of which can influence the rate of BD. While we screened a large cohort of subfertile men and compared them against a large registry of BD, a larger study would permit an analysis for specific types of congenital anomalies given the low frequency of specific BDs. Finally, BDs are only recorded in the TBDFR and generate fetal death certificates if the period of gestation is 20 completed weeks or more. Thus, our study cannot comment on BDs that may have occurred prior to 20 weeks of gestation resulting in a spontaneous abortion, as reporting of these is not mandated by the state.

While the semen analysis remains a cornerstone in the evaluation of male infertility, it is a poor predictor of BDs in stillborn or live offspring. While higher rates of cardiac and renal malformations may be present in the children of men who have undergone male fertility evaluation, additional study is required to definitively determine this association.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Acknowledgements

The authors are grateful to Karen Moffitt, MPH, for extensive work in linking the datasets underlying this project.

Authors' roles

A.W.P. and A.S.H.: conception, design and acquisition of the data, M.L.E., P.H.L.: statistical analysis. All authors contributed to the analysis and interpretation of the data. A.S.H. and A.W.P. wrote the article, which was critically revised by all authors. All the authors approved the submitted version.

Funding

Supported in part by the NIH Men's Reproductive Health Research (MRHR) K12 HD073917 (D.J.L.), the Multidisciplinary K12 Urologic

Research (KUR) Career Development Program (D.J.L.), P01HD36289 from the Eunice Kennedy Shriver National Institute for Child Health and Human Development, NIH (D.J.L.), and by U01DD000494 from the Centers for Disease Control and Prevention and the Title V Block Grant to the Texas Department of State Health Services. A.W.P. is a National Institutes of Health K08 Scholar supported by a Mentored Career Development Award (K08DK115835-01) from the National Institute of Diabetes and Digestive and Kidney Diseases. This work is also supported in part through a Urology Care Foundation Rising Stars in Urology Award (to A.W.P.).

Conflict of interest

None of the authors has a conflict of interest.

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